PRECISION NUTRITION &

Advanced Culinary Medicine

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This electronic textbook (eBook) and/or eBook chapters are designed to accompany NS801, Precision Nutrition and Advanced Culinary Medicine, a 1-credit, 8-week online medical elective course for the University of Kentucky College of Medicine Office of Medical Education curricula. Reading for the course will be labeled to align with the content of the online course; such that Module 2 is aligned with Chapter 2, Module 3 with Chapter 3, and so on. As an open access textbook supported by the University of Kentucky Libraries Alternative Textbook program, all sources will be linked and readily available.

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Precision Nutrition & Advanced Culinary Medicine E-Book

Modules 1-3

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INTRODUCTION

Precision nutrition is an emerging field with limited application at the time of this eBook construction. Scientific advancements and research in precision nutrition currently exceed the application that is evident in many clinical settings. Precision nutrition depends on scores of data from patients, including but not limited to genetic, microbiome, anthropometric, cultural influences, personal preferences, etc. Despite the data requirements, the utility and effectiveness that could underlie precision nutrition in practice is astounding. **There is not one diet that "works" for everyone, but there is a dietary pattern that works for each person.** (The word "works" is used to infer optimization of health and wellness while reducing disease risk.) The reality of this statement becomes apparent when reviewing the research, that Clinical Nutrition research, that illustrates disparate outcomes despite participants strictly adhering to the same dietary protocols.

Culinary medicine is not dietetics, internal medicine, nor is it a culinary school. Instead, **culinary medicine** is an evidence-based field that aims to educate and inform patients and practitioners about culinary strategies to put nutrition recommendations into practice. Culinary medicine courses emerged in medical education in 2003 in upstate New York. Since that time, culinary medicine courses have been integrated into medical schools across the nation, mostly as elective courses. Culinary medicine offers ways to understand and appreciate the patient's understanding of food and cooking as part of his or her care and apply that understanding to a patient's health care goals.

Bridging precision nutrition and culinary medicine takes the latest nutritional sciences research around individualized nutrition and combines it with practical strategies for implementation in the kitchen.

Culinary Exercise Preparation

Preparing for culinary exercises means becoming familiar with elements of food preparation and cooking, such as measurement (quantitative and qualitative), food safety, and knife skills. This chapter will introduce and explore these concepts to facilitate a knowledgeable, effective, and safe culinary experience.

Measurements in the Kitchen

Measurement is essential to critical fields of study and inquiry, such as mathematics, physics, and chemistry. While the stakes are not as high in culinary practice as compared to quantum physics or structural engineering, measurement remains essential in cooking and culinary practice. Every measurement provides three kinds of information: the size or magnitude of the measurement (a number); a standard of comparison for the measurement (a unit); and an indication of the uncertainty of the measurement. The number and unit are explicitly represented when a quantity is written. As an example, a bag of rice is 5 kg (11 lb.). Five (5) is the number and kg, or kilogram, is the unit of measurement. The metric system provides the most widely used units of measurements in the world; the International System of Units (SI) is based on the metric system. The U.S. Customary System is also widely used in the United States for culinary processes and food preparation (Table 2.1). Accurately converting between these two systems of measurement (see Table 2.2) is important for the sake of any recipes where units need converting. Recipes referenced in NS801 will utilize the U.S. Customary System of Units.

Table 2.1: The Most Common Units of Measurements in Culinary Processes

MEASUREMENT	**International System of Units, SI**	**U.S. Customary System of Units**
LENGTH	meter (m)	inch (in)
VOLUME	liter (L); meter cube (m^3)	fluid ounce (fl oz); gallon (gal); quart (qt)
WEIGHT	gram (g)	pound (lb); ounce (oz)
TEMPERATURE	Celsius,	Fahrenheit

Table 2.2: Common Conversion Factors for the Length, Volume, and Weight Measurements

MEASUREMENT	**CONVERSION FACTOR**
Length	1 in. = 2.54 cm 1 m = 100 cm
Volume	1 L = 1,000 mL 1 L = 33.8 fl. Oz (U.S.) 1 L = 0.264 gal (U.S.
Weight	1 kg = 1,000 g 1 lb = 454 g 1 lb = 16 oz (U.S.)

The Case for Food Safety at Home

Foodborne illness is 100% preventable, and yet, 56,000 people per year become ill from foodborne causes in the United States, creating high economic costs, loss of productivity and reduced quality of life for many. Experts agree that the home is the primary location where foodborne outbreaks occur; however, many consumers do not believe the home to be a risky place. **Health care professionals need to be aware of consumers' food safety attitudes and behaviors in the home and deliver tailored food safety interventions. Small steps and minor actions can prevent foodborne illnesses.**

In recent years, headlines, and news flashes on widespread outbreaks of foodborne disease caused by lapses in food safety or emerging pathogens have provided vivid reminders that food not only nourishes and sustains us, but if handled unsafely, can be a major threat to health and well-being. According to FoodNet, the United States' food safety report card, considerable progress had been made toward decreasing foodborne illnesses caused by key pathogens, except for Salmonella. The decline is good news, but this rate is still higher than Healthy People 2020 goals, and many people continue to suffer the ill effects of foodborne illness. Experts estimate that each year 1 in 6 Americans experience foodborne illness—resulting in of the known hospitalizations of 56,000 and death of more than 1,300.

Home is the location most often associated with significant foodborne illness risk. This is because a vast majority of food eaten is prepared at home, thereby increasing the opportunities for food handling errors to occur. The emphasis frequently placed on how often people "eat out" causes many to not realize that the home food environment provides 72% of the food, by weight, consumed by Americans and accounts for 93% of the food consumed by those who eat most meals at home.

Health professionals should be aware that there are select groups of people who are at increased risk of foodborne illness, such as generally young and older populations, pregnant women, etc. And these groups make up a sizable portion of the population. For example, 13% of Americans are 65 years and over, 7% are less than 5 years old, and almost 4 million women (about twice the population of New Mexico) are pregnant every year, and 1% is immunocompromised due to disease, medical treatment, and/or organ transplant. In addition to this, 12 million people are receiving healthcare at home as an extension of or replacement for traditional in-patient care. This amounts to one quarter of the U.S. population being at increased risk for foodborne disease and at elevated risk for severe health outcomes if they become ill.

Many consumers—even those in high-risk groups—do not perceive themselves or someone in their families to be susceptible to foodborne illness, rank their risk of foodborne illness lower than that of others, or do not follow all recommended food safety practices. Consequently, they do not take enough precautions. For instance, young infants are particularly vulnerable to infections due to their immature immune systems which makes scrupulous cleaning and handling of equipment associated with infant feeding critical. Although women report they become

interested in food safety after they have a baby, there are numerous documented food handling mistakes regarding infant feeding. Researchers in the United Kingdom, for example, found that 4% of baby bottles that parents indicated had been cleaned, disinfected, and ready to be filled were contaminated with Staphylococcus aureus.

Additionally, food prepared in the home may be served to a wider community, such as at bake sales, church dinners, and school picnics. Even foods children trade at lunchtime or homemade snacks adults share with colleagues in the workplace can be a source of foodborne illness. Food samples served at farm market stands also are commonly prepared in home kitchens. At least one-fifth of young children in the United States also are in home-based (non-parental) child-care where food may be served. Unlike commercial enterprises, home kitchens are multipurpose areas and are much more than just food preparation and storage places. For instance, researchers have observed women's purses that once sat on public ladies' restroom floors were sitting on kitchen counters. Pets, old newspapers, dirty laundry, house plants, and soil all are common in-home kitchens—one research team even reported observing a home kitchen where automotive repairs were occurring. Kitchen sinks are used for hand washing, produce washing, dishwashing, soaking clothing, washing children and pets, and wetting mops. Dirty dishes may be stacked alongside clean dishes on kitchen counters. Raw unwashed vegetables, dripping raw meat, as well as cooked ready-to-eat foods are common in home refrigerators. The multiple uses of home kitchens potentially introduce an array of pathogens that can spread to foods, proliferate, and result in illness. Some of the pathogens that have been confirmed in home kitchens include Salmonella, pathogenic Escherichia coli, S. aureus, and Campylobacter. At least two studies have reported that the kitchen is more heavily contaminated with fecal coliforms than bathrooms.

On the positive side, about 6 in 10 consumers recognize they are responsible for food safety, and nearly all agree that they gave at least some thought to food safety in the past year. But there are gaps in consumer applications of Clean, Separate, Chill, and Cook advice from the Dietary Guidelines for Americans and food safety programs like Fight Bac! Inconsistent practices among home food handlers can negate much of the effort made in improving and maintaining food safety achieved earlier in the food chain.

Principles of Food Safety at Home

The main principles of food safety discussed herein include Clean, Separate, Chill, and Cook.

I. Clean

The goal of "clean" is to prevent cross contamination—or the transfer of disease-causing microorganisms from one food, object, or surface to another food—by washing hands, food contact surfaces, and kitchen equipment. Hands are a major vehicle for spreading pathogens around the kitchen—thus hand washing is critical to preventing cross contamination. Survey data indicates that almost all consumers report washing their hands with soap for a full 20 s before preparing food all or most of the time. Most consumers also report they often or always wash their hands after handling raw meat. Despite consumers' awareness of the importance of hand washing, they are not washing their hands thoroughly. For example, after handling raw chicken, 73 to 100% of hands of consumers who reported washing their hands after touching the meat in a research study were contaminated with Campylobacter jejuni. None of the consumers sufficiently washed their hands to prevent C. jejuni transfer to salads after handling the raw chicken. Little is known about how often during meal preparation consumers wash their hands. Given how often the most heavily contaminated areas in the kitchen (i.e., refrigerator handles, tea kettle handles, tap handles, sink drain areas, dishcloths, and sponges) are touched during meal preparation, it is possible, if not likely, that hands are not washed frequently enough to prevent the transfer of pathogens to ready-to-eat food, food packaging, or equipment and contact surfaces used to prepare food.

Dishcloths, kitchen rags, and cleaning sponges quickly become heavily contaminated with a diverse array of microbes, harboring, and spreading contamination to hands, kitchen equipment, and contact surfaces. High numbers of E. coli survive in dishcloths for at least 48 h. Consumers have room for improvement when using sponges and sanitizing dishcloths—of the 92% of consumers who use them, just 9% report changing dishcloths or sponges daily, 44% change them at least weekly, the remainder change them less often, with 5% waiting until they fall apart. Kitchen utensils and cutting boards also are key cross contamination routes. In fact, research in the United Kingdom suggests that 14% of all foodborne illnesses may be due to inadequately cleaned cutting boards and knives. Although nearly all consumers report they wash these items after using them with raw meat or produce, observational data indicate that most consumers do not clean cutting boards and utensils sufficiently to prevent cross contamination. Cleaning of food products prior to consumption and preparation is another vital component of "clean". A recent study recommended that consumers use a 3% hydrogen peroxide solution (which is readily available at pharmacies) to wash cantaloupes prior to cutting. A misperception remains that washing raw poultry removes "germs," hence providing clear and accurate information regarding which food products require washing (and how to properly do so) before preparation is needed.

A new cross-contamination vehicle that has the potential to pose a significant risk of bacterial cross contamination is the reusable grocery bag. One in three consumers report using these bags

for more than just groceries —they double as gym bags, toy bags, and other uses. This is a concern given that 75% of consumers use these same bags for carrying raw meat and other foods. Large numbers of bacteria (including fecal coliforms) were found in every reusable bag collected from consumers outside a grocery store, but none were found in new bags or traditional plastic bags. Despite the effectiveness of removing pathogens by washing reusable grocery bags, only 3% of consumers reported regularly washing them. Dirty reusable grocery bags could pose a foodborne illness risk—an outbreak of norovirus in a girls' soccer team was traced to a contaminated reusable grocery bag

II. Separate

"Separate," like "clean," is vital to preventing cross contamination. The goal of "separate" is to keep raw meat, poultry, and seafood separate from ready-to-eat foods like salads and cooked meat. About three-quarters of consumers report keeping raw meat, poultry, and seafood separate from ready-to-eat food products, and nine in ten use different plates for raw and cooked meat. However, there is room for improvement, especially considering that meat, poultry, and seafood are the leading causes of foodborne illness.

III. Chill

"Chill" focuses on the refrigerator's critical role in temperature control. But it is important to also think about "clean" and "separate" in this appliance. Studies indicate that refrigerators in many households are not clean. One study from Ireland reported that more than half of the refrigerators swabbed had at least one of these pathogens: S. aureus, Salmonella enterica, E. coli, Listeria monocytogenes and Yersinia enterocolitica. Many refrigerators are also not cool enough, with average temperatures exceeding the recommended 40 °F (5 °C).This problem has been noted in the U.S., U.K., Ireland, New Zealand, and Australia. Compounding the cooling problem is that refrigerators often are packed so tightly with food that air circulation is restricted. Tight packing also increases food-to-food cross-contamination risk. Only one-quarter of consumers report regularly checking refrigerator temperatures, and another quarter do not even have a refrigerator thermometer. One positive note is that 60% of those in the U.S. know the safe temperature for refrigerators to be less than 40 °F (5 °C). Another aspect of "chill" is keeping perishable foods out of danger zone temperatures. Most consumers (79%) reported leaving prepared perishable food at room temperature no longer than the recommended 2-hour timeframe and two-thirds report thawing food in the refrigerator. There also is a common misconception that cooked foods should be cooled to room temperature before being placed in the refrigerator.

IV. Cook

Among the four principles discussed here, the greatest area needing improvement is "cook"—according to Healthy People 2020, only about 37% of consumers achieve the goal of heating foods, such as meat and poultry, to a temperature sufficiently high enough to kill harmful pathogens. Almost 9 in 10 consumers know that ground beef should be cooked to at least 160 °F

(71 °C) and two-thirds report they usually cook meats and poultry to this temperature. However, most do not know that color is not a good indicator of doneness and less than a quarter validate the accuracy of the cooking temperature with a thermometer. Consumers continue not to use thermometers despite knowing that the greatest food poisoning risk is from undercooked foods and that "germs" in food are serious dangers. Many consumers report that thermometers are inconvenient and difficult to use, especially with small cuts of meat, which contributes to low rates of thermometer use. Many express frustrations with needing to remember the different temperature recommendations for beef, poultry, and seafood. Also, recipes and cooking show seldom give endpoint temperatures —recommending color as an indicator of meat doneness three times more often than temperature. Color recommendations and lack of thermometer use in televised cooking shows may lead consumers to view using food thermometers as a sign of being an inexperienced cook. But visual inspection is risky—for instance, 70% of the chicken pieces consumers judged as "done" by visual inspection had not reached recommended cooking temperature and had active C. jejuni cells. Microwave ovens are ubiquitous in-home kitchens throughout the developed world and play a key role in achieving the "cook" goal. Many consumers report that they regularly follow cooking, flipping, rotating, stirring, and standing instructions and check to be sure food is fully heated before eating. However, few use a thermometer to verify food has been sufficiently heated in a microwave. In addition, microwave ovens are seldom cleaned and present a cross-contamination risk.

V. A Note on Risky foods

A fifth category of food safety practices that typically is not part of most food safety campaigns is eating "risky" foods. Substantial proportions of the population consume foods that pose a significant foodborne illness risk, such as undercooked animal flesh. For instance, more than half of U.S. consumers report eating raw cookie dough (made with raw eggs), two-fifths consume raw eggs, a quarter eat raw fish, one-fifth eat undercooked hamburgers, and an eighth eat raw oysters.

Four Practical Strategies for Health Professionals to Promote Food Safety

I. Boost knowledge

For behaviors associated with the primary principles of food safety (Clean, Separate, Chill, and Cook), many consumers are aware of the food safety basics (wash your hands, cook pork thoroughly, etc.). Consumers also understand that germs - even in food - can be harmful. However, many consumers have food safety knowledge gaps, and their knowledge of safe food handling practices does not always correspond with reported use and practical application. This suggests a need to build consumer knowledge, activate existing knowledge, and motivate information application and practice.

II. Highlight responsibility

Consumers are less likely to take protective steps if they believe their risk of foodborne illness is controlled by fate or luck, and when minimizing their responsibility to that of others in the food safety chain. Some feel they have little responsibility because they believe most foodborne illnesses are caused earlier in the food safety chain or by retail food establishments. Helping consumers understand the magnitude of control they have in their own homes as food safety risk managers and finding motivators—such as helping them understand that by using a thermometer, loved ones are less likely become sick from undercooked meat or showing them how easy thermometers are to use—can help promote behavior change.

III. Bring awareness to susceptibility and severity

Engaging in health protective behaviors is associated with greater perceived susceptibility or beliefs in the likelihood of a negative health outcome and its severity. For example, those who believe food poisoning is a personal threat eat risky foods less often or not at all. Personalizing risks can help consumers better understand their own foodborne illness susceptibility. Thus, interventions should help consumers learn who is at increased risk for foodborne illness as better knowledge of these groups predicts better compliance with safe food handling recommendations.

IV. Suggest cues to action

Researchers have reported that consumers take food safety precautions only when they perceive a risk, such as when they handle raw poultry, fear they may give others food poisoning, or when others are watching. At other times, consumers may be acting out of habit and make food handling mistakes because they lack “cues to action”. Fein and colleagues use the analogy of driving a car—drivers are constantly taking protective actions in response to cues, such as the yellow stripe in the middle of the road or a stop sign. But, when preparing and cooking food, hazards are not visible (e.g., pathogens on the unwashed produce that contaminate the counter and our hands) and there are few, if any, cues to remind us to practice safe food handling. Risk messages or handling instructions on food packages can help to cue some to change their behavior. In one study investigating cues to protective food safety behaviors, the control group received a chicken salad recipe, and the experimental group received the same recipe with a

printed message encouraging them to take great care to avoid cross contaminating the salad by preventing raw meat juices from encountering other ingredients and utensils. Interestingly, salads made by the group receiving the cue had significantly less bacteria than those made by the control group, putting the experimental group at a four-fold lower relative risk of falling ill than the control group. Another study that involved preparing a chicken salad recipe found that only 57% of important hygiene measures (e.g., washing hands with soap and water, checking doneness with a thermometer) were used by participants. Adding food safety cues to food packages may be particularly effective, given that half of consumers indicate they commonly read cooking instructions on food packages [57]. Practical cues that could be shared with patients for implementation in the home kitchen include:

- Placing soap dispensers in direct line of sight to help improve hand washing [164].
- Printing washing instructions on reusable grocery bags could cue consumers to wash them.
- Distributing a quick reference guide for endpoint cooking temperatures of various proteins. Keeping the endpoint temperatures within sight of the cooking area could increase temperature checking.
- Adding endpoint cooking temperatures in recipes and cookbooks.

Knife Skills

This chapter includes information on how to choose knives, take care of them, and cut almost anything (but please, do not cut yourself!). Information herein may not confer the heightened knife skills that you might take away from culinary school, but they are the skills that home chefs and cooks consider the easiest, quickest, and safest paths to preparing the food we want to cook.

How to Hold a Knife

The gripping hand (or cutting hand), which grips the knife, has the star turn, but the other hand is an important supporting player. The helping hand holds, nudges, and stabilizes the ingredient being cut, to maximize safety and efficiency.

Gripping Hand: For the knife grip used by most chefs, the palm of the hand chokes up on the handle, while the thumb and index finger grip the top of the blade. This is different from how many home cooks hold a knife, by wrapping the entire hand around the handle. The chef's grip has evolved that way for a reason: it is the most efficient way to use the weight of the knife, the sharpness of its blade, and the strength of your arms, which makes for the easiest cutting.

Helping Hand: The ideal position for the helping hand is called the bear claw, with the fingertips curled under and knuckles pressing down on the ingredient to keep it from rolling or sliding. It may feel odd, but it is the safest place for your fingertips to be in relation to the cutting blade. Alternatively, bunch your fingertips together and rest the pads on top of the ingredient.

In a perfect world, while the hand that is holding the knife moves forward and back to cut, the helping hand moves across in even increments, creating perfect slices. (Do not despair; this takes practice and is hardly a requirement for home cooks.)

Tips for the Grip:

Overall, the best way to handle a knife is the way it feels safe to you. Here are a few principles to live by:

1. The knife handle should not be held in a death grip: try to relax hands and wrists and let the blade do the cutting.
2. Position all 10 fingers so it is impossible for the blade to cut them.
3. The hand holding the knife should be gripping the blade as well as the handle.
4. The knife moves in a rocking motion, from front to back, as well as up and down.
5. The knife should be at the same height or just below your elbows, so that the whole upper body, not just the hands, can put downward pressure on the knife.

The Cuts:

- Chop

If a basic task like chopping carrots takes forever, it can make cooking seem like a punishment. That's why becoming efficient with a knife is so helpful. And in that effort, chopping is your greatest ally. Unlike professional chefs, who routinely dice their ingredients into measured cubes, home cooks can usually keep it rough, if all the pieces end up about the same size.

- Dice

More exact than chopping, dicing is the process by which vegetables and fruits, in all their irregular and lumpy glory, are turned into small, neat cubes that cook uniformly. Whether chefs are prepping a giant potato or a baby carrot, they reduce the curves and bumps to cubic shapes. When that cube is cut along horizontal and vertical lines, neat dice is the result. The videos linked in our online course demonstrate larger to smaller diced ingredients.

- Slice and Cut

When cutting ingredients into larger pieces – like a round slice of tomato, lemon or cucumber, or a wedge of apple – the choice of knife and how it moves most often depend on the texture of the ingredient. Although a super-sharp chef's knife can be used to slice a tomato or lemon in quick downward strokes, many home cooks will prefer the controlled back-and-forth sawing motion of a serrated knife. Either way, the goal is to have smooth slices of even thickness.

- Chiffonade and Julienne

Home cooks are most likely to use these long, slim cuts for ingredients that are going into stir-fries and salads, for tough greens destined for the cooking pot, or to make fluffy garnishes from soft herbs and scallions. They are also useful for making raw vegetable platters look their most elegant.

Your Basic Knife Drawer:

In any craft, having just the right tool for the job makes the task easier. In cooking, there are knives for specific tasks like carving, filleting, and slicing. But with just a few versatile knives, you can perform virtually any task in the kitchen. These are the knives you will use most often in your kitchen. With these three, you can perform almost any task.

- **Chef's knife:** A classic chef's knife, with its broad, tapering blade, sharp tip and chunky handle is the workhorse of the kitchen. Practicing with one really will make you a better cook: they are sharper, stronger and they do more of the work for you than smaller knives. For many home cooks, an 8-inch blade with a plastic handle is perfect, especially to start. Work up to a 10-inch knife, which is more efficient overall. When buying, look for a comfortable handle and a blade that is thicker at the base than at the tip.
- **Utility knife:** These small knives are in constant use in most home kitchens, so it's worth having three or four. Many home cooks use these knives for every job: their short blades, 3 to 4 inches long, make them easier to control. They are best for small soft ingredients like shallots, mushrooms, and peaches. Inexpensive thin-bladed knives with plastic handles are often the most practical choice. Small knives are difficult for home cooks to sharpen, and so simply replacing them when they get dull is nothing to be ashamed of.
- **Serrated knife:** A large, serrated knife (a 10-inch blade is standard) is useful not only for slicing bread but for sawing through ingredients with firm rinds like butternut squash, lemons, watermelon, and pineapples. The scalloped forefront makes neat slices of soft-skinned ingredients like tomatoes and eggplants.

Sharpening and Storage

How often do you sharpen your knives? Home cooks have a lot of things to take care of, and knives do not often make it to the top of the list. But keeping knives sharp saves time eventually, and it keeps you safe as well: sharp knives cut, but dull knives slip. This eBook will tell you how to sharpen and hone your knives (both necessary) and how to store them. Associated videos are available on the NS801 course shell.

Sharpening

Once a knife is dull – test it by drawing the blade along the edge of a piece of paper to see if it cuts – it needs to be sharpened. We strongly recommend using manual, not electric sharpeners. It is too easy to get carried away, exerting too much pressure, and making too many strokes, while the whirling machine eats the edge of your knife. With a manual sharpener, use gentle pressure while pulling the knife through, and test often as you go.

Honing

Many people do not know the difference between honing and sharpening. But they are equally important for efficient knife work. Honing, which makes the blade of a knife straight, is done with what is often (and incorrectly) called a sharpening steel, by drawing the blade over and over along an abrasive rod of metal, ceramic, or stone. Many professionals hone their chefs' knives daily but doing it weekly is plenty for most home cooks. It is a quick process once you feel confident – and it's fun, making you look, feel, and sound like a serious cook. But remember honing helps maintain the blade's sharpness but does not actually sharpen it.

Tips for Knife Care and Storage

1. Do not wait until a knife gets dull before taking care of it. The easiest system involves keeping your knives sharp in the first place, by giving them a quick honing and sharpening every few weeks.
2. Use a cutting surface that will not dull them. Glass cutting boards are much too hard. Wood is gentlest, and thick plastic is next best. Make sure boards stay firmly in place on the counter by laying a kitchen towel underneath.
3. For storage, prevent nicks — including microscopic ones that dull the blade — by keeping knives away from one another. Store them in a block or on a magnetic strip; place them in a drawer if you do not want to use counter or wall space.
4. There is no reason a knife with a synthetic handle and a stainless-steel or ceramic blade cannot be safely washed in the dishwasher — but you must place them so the knife cannot get jostled around or the edge cannot be chipped. But knives with wood handles, high-carbon-steel blades and other sensitive materials should be washed by hand.
5. Small utility knives with very thin, flexible blades cannot be sharpened, so it is best to find an inexpensive type that you like and replace them often. Serrated knives cannot be sharpened either, so keep them out of harm's way.

3. Emerging Concepts in Precision Nutrition

Adequate nutrition is essential to life. Beyond this, nutrition is a key factor for the prevention, mitigation and treatment of various diseases and health conditions. Hippocrates, known as the father of modern medicine, once said: "Let the food be thy medicine and the medicine be thy food." Since the days of Hippocrates, the understanding of nutrition and nutritional sciences, and the mechanisms by which nutrients can modulate cellular signaling responses and affect health risks, have been dramatically broadened. Food and nutritional scientists continue to explore and investigate mechanisms by which nutritional components can either prevent or induce characteristics of various disease states, in hopes of identifying key levers in the fight against conditions such as diabetes, cancer, and Alzheimer's disease. Some of the most consistent and common nutritional guidelines include the messages in Table 3.1.

Table 3.1 Evidence-based & well-established dietary recommendations
1. Establish healthy limits for salt (sodium), added sugar, and saturated fat.
2. Use portion control, or calorie limits
3. Drink plenty of water
4. Consume plenty of fresh or frozen fruits and vegetables.

The Dietary Guidelines for Americans (DGA) are a set of dietary recommendations based on the latest scientific research that is updated every five years. Yet, clinical nutrition research has shown repeatedly that dietary protocols for one cohort of consumers yield different outcomes in another. The totality of distinctions and differences from person to person in terms of genetics, microbiome, and lifestyle make the case for personalized nutritional recommendations that consider all such information. **Precision nutrition** in research and practice considers multiple levels of influence that define an individual's specific dietary needs, such as genetic background, microbiome, metabolism, physical activity, environmental exposures, and other factors. Precision nutrition focuses on the individual rather than groups of people, in stark contrast to the DGA. Thus, precision nutrition considers not only "healthy" foods, but the "right" foods for an individual. Is it possible that what is beneficial to one person may not be beneficial for another? The field of precision nutrition says "yes" to that question.

This chapter will explore emerging concepts in precision nutrition, which will be further explained within additional chapters of this text. Understanding the inter-relationships between these will be important for developing targeted and specific dietary interventions to improve the health of an increasingly diverse U.S. population. The underpinning goal of precision nutrition is to reveal the precise amounts of macro and micronutrients needed to achieve the maximum health benefit on an individual level. Another theory supporting precision nutrition is that optimizing the intakes of specific nutrients could maximize their individual and collective effects.

Defining Precision Nutrition

In general, precision nutrition is thought to include three important tenets:

1. The provision of nutritional advice adapted to an individual's unique internal and external influences. It is a specially tailored recommendation of a dietary habit for an individual to maintain good health and lifestyle and prevent disease.
2. Precision nutritional interventions can only be effective if they translate into behavioral change towards a healthy lifestyle.
3. Precision nutrition should be applicable to healthy individuals as well as patients afflicted with, or susceptible to, specific medical conditions.

Because of its origins during the period of genomic sequencing, the term still partially overlaps with some closely related terms such as nutrigenomics, nutrigenetics, gene-food interactions, etc., but precision nutrition is multifaceted and includes an individual's behavior, dietary habits/cultural influence, food availability, phenotypic and genetic makeup, metabolism and even the microbiome. (Maulik) Indeed, precision nutrition evaluates one's DNA, microbiome, and metabolic response to specific foods or dietary patterns to determine the most effective eating plan to prevent or treat disease. The specific dietary recommendations based on genetic, metabolomic, or microbiome-based information in this text will be identified throughout this eBook with a **PN** notation.

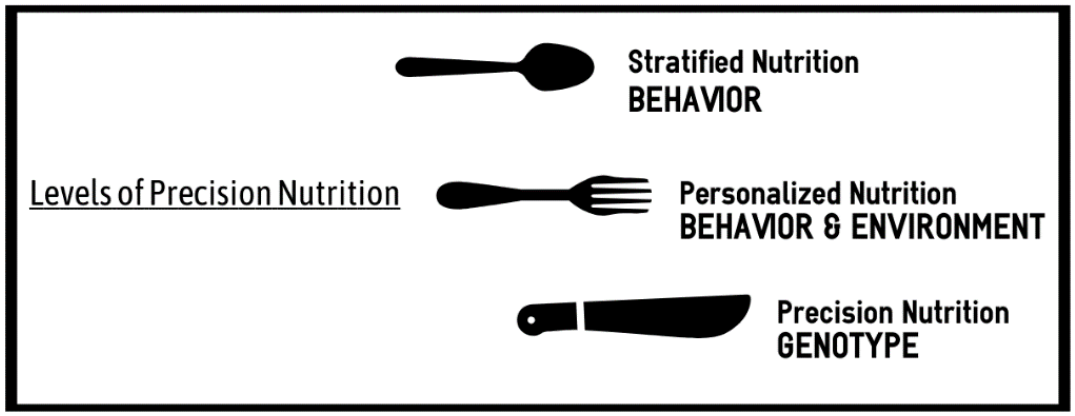
Multiple terms and definitions are used during discussions of precision medicine and nutrition, sometimes without clarity on details. In addition to the term precision nutrition, many other terms are used— for example, personalized nutrition, stratified nutrition, tailored nutrition, and individually tailored nutrition (Table 3.2; adapted from Table 2.1 in Maulik).

Table 3.2 Terms to Describe Precision Medicine & Precision Nutrition
Precision nutrition is the most ambitious of the descriptors. It suggests that it is possible to have enough quantitative understanding about the complex relationships between an individual, his/her food consumption, and his/her phenotype (including health) to offer nutritional intervention/advice, which is known to be individually beneficial. The degree of scientific certainty required for precision nutrition is greater than that required for other approaches.
Stratified and tailored nutrition are similar. These approaches attempt to group individuals with shared characteristics and to deliver nutritional intervention/advice that is suited to each group.
Personalized nutrition and individually tailored nutrition mean similar things and more specifically attempt to deliver nutritional intervention/advice suited to everyone.
Nutrigenetics is an aspect of personalized nutrition that studies the different phenotypic responses (e.g., weight, blood pressure, plasma cholesterol or glucose levels) to a specific diet (e.g., low fat or Mediterranean diets), depending on the genotype of the individual.
Nutrigenomics involves the characterization of all gene products affected by nutrients and their metabolic consequences.

Exposome is the collection of environmental factors, such as stress, physical activity, and diet, to which an individual is exposed, and which may affect health. As one moves from stratified to personalized to precision nutrition, it becomes necessary to apply more and more dimensions or characteristics to achieve the desired goal. For example, stratification could be undertaken using one, or a few, dimensions such as age, gender, or health status. In contrast, given the complexity of relationships between individual diet and phenotype, deployment of a wide range of dimensions/characteristics, perhaps including "big data" approaches, would be necessary to achieve the goal of precision nutrition. An exception to this broad generalization is the management of inborn errors of metabolism such as phenylketonuria, where "precision nutrition" can be achieved using information on a single characteristic— that is, genotype.
Epigenomics is a branch of genomics concerned with the epigenetic changes (methylation, histone modification, microRNAs) that modify the expression and function of the genetic material of an organism.
Metabolomics is the scientific study and analysis of the metabolites (usually restricted to small molecules, e.g., < 900 Daltons) produced by a cell, tissue, or organism.
Microbiomics is the study of microbiome, the totality of microbes in specific environments (e.g., the human gut).

According to the International Society of Nutrigenetics/Nutrigenomics, there are three overall levels of precision nutrition, with stratified being the most generalizable, followed by individualized and then genotype-directed (Figure 3.1).

Figure 3.1. Three levels of Precision Nutrition



Nutrient-Gene Interactions

The diet-gene interaction is the most researched aspect of the field, with several examples of researched gene-food interactions published to date. (Table 3.3) Though individuals share most of their genes in common, the few differences are enough to cause significant alterations in phenotype, including the way individuals respond to their diet. Changes to phenotype may evoke changes in behavior, physiological characteristics, or susceptibility to diseases as well. Of these genetic differences held accountable for phenotypic diversity, it is increasingly apparent that **single nucleotide polymorphisms (SNPs)**, the most known and common genetic variations between human beings, will be a key factor. The study of diet-gene interactions can be loosely sub-classified into two distinct study areas: nutrigenetics and nutrigenomics.

Nutrigenetics deals with how genetic makeup influences the way nutrients are acquired, metabolized, and stored, while nutrigenomics is the study of how food components influence gene expression. Nutrigenetics plays more of a preventative role, delineating the foods that should be avoided because they could place the individual at risk for disease. On the other hand, **nutrigenomics** also has the potential to transform diet into a therapeutic tool to treat diseases, like pharmaceutical drugs. It is based on identification of genetic risk factors and targeting of key players of gene expression at any given stage, to up or downregulate the effects of certain genes.

Table 3.3. Genetic Variants Effect Health Outcomes Associated with Specific Dietary Factors.

GENETIC VARIANTS THAT MODIFY THE LINK BETWEEN DIETARY FACTORS & HEALTH OUTCOMES			
Gene	**Function**	**Dietary Factor**	**Health Outcomes**
CYP1A2	Encodes CYP1A2 liver enzyme; metabolizes caffeine; identifies individuals as fast or slow metabolizers	Caffeine (Coffee, tea, soda, energy drinks, caffeine supplements)	Cardiovascular health endurance
ADORA2A	Regulates myocardial oxygen demand; increases coronary circulation via vasodilation	Caffeine (Coffee, tea, soda, energy drinks, caffeine supplements)	Vigilance when fatigued, sleep quality
BCMO1	Converts pro-vitamin A carotenoids to Vitamin A	Bluefin tuna, hard goat cheese, eggs, mackerel, carrots, sweet potato	Visuo-motor skills and immunity
HFE	Regulates intestinal iron uptake	Iron (beef, chicken, fish, organ meats, almonds, spinach)	Hereditary hemochromatosis
TMPRSS6	Regulate the peptide hormone hepcidin, which controls iron absorption	Iron (beef, chicken, fish, organ meats, almonds, spinach)	Iron-deficiency risk

FUT2	Involved in vitamin B12 cell transport and absorption	Vitamin B12 (Clams, oysters, herring, nutritional yeast, beef, salmon)	Megaloblastic anemia and hyperhomocysteine mia
GSTT1	Role in vitamin C utilization via glutathione S-transferase enzymes	Vitamin C (red peppers, strawberries, pineapple, oranges, broccoli)	Circulating ascorbic acid levels mitigate exercise-induced ROS production
GC and CYP2R1	GC encodes vitamin D-binding protein, involved in binding and transporting vit D to tissues; CYP2R1 encodes the enzyme vitamin D 25-hydroxylase involved in vit D activation	Vitamin D (salmon, white fish, rainbow trout, halibut, milk)	Circulating 25 (OH) D levels effect immunity, bone health, inflammation, strength training and recovery

The Microbiome

IOM (Institute of Medicine). 2013. *The human microbiome, diet, and health: Workshop summary.* Washington, DC: The National Academies Press.

Table 3.4 KEY TERMS THAT HELP DEFINE AND DESCRIBE THE MICROBIOME	
Commensal:	An organism participating in a symbiotic relationship in which one species derives some benefit while the other is unaffected
Enterotype:	The concept that distinct communities of bacteria are defined by their bacterial composition (Arumugam et al., 2011)
Metabonomics:	The quantitative measurement of the multiparametric (time-related) metabolic responses of complex systems to a pathophysiological stimulus or genetic modification (Nicholson et al., 1999); often used synonymously with **metabolomics** (Fiehn, 2002)
Metagenomics:	The study of the gene content and encoded functional attributes of the gut microbiome in healthy humans (Gill et al., 2006)
Microbiome (human):	The full complement of microbes (bacteria, viruses, fungi, and protozoa), their genes, and genomes in or on the human body
Prebiotic:	A substance that (1) is resistant to gastric acidity, to enzymatic hydrolysis, and to gastrointestinal absorption (i.e., not hydrolytically digestible); (2) is fermented by cecal-colonic microflora; and (3) selectively stimulates growth and/ or activity of those bacteria that contribute to colonic and host health (Gibson et al., 2004) *or* a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota (Pineiro et al., 2008)
Probiotics:	Living microorganisms that, when administered in adequate amounts, confer a health benefit on their host (FAO-WHO, 2002)
Resistome:	The collective informational resources available to the microbiome for responding to antimicrobial pressure (Wright, 2007)

Microbiome-derived recommendations for Precision Nutrition: A Primer

As defined in the table above, the microbiome is the collective complement of microbes (bacteria, viruses, fungi, and protozoa), their genes, and genomes in or on the human body. Emerging research ties functions of the microbiome to variable aspects of health and disease. The microbiome is influenced by food, and food influences the microbiome. There is an interesting interaction between nutrition and dietary patterns and microbiome fluctuations that scientists are trying to unravel. Given the individualistic nature of each person's microbiome, it has emerged as an important factor to consider in precision nutrition. Microbiome testing, where fecal samples are evaluated, is another layer of testing to provide individualized information that might influence precision nutrition recommendations. As outlined below, this concept of using microbiome-centric data to predict physiological outcomes due to diet depends on the acquisition and analysis of data.

Figure 3.2 below illustrates the concept of human study participants adopting a dietary intervention and then undergoing microbiome analysis, with these data being parsed out according to a response. Data from responders and non-responders would be analyzed with the goal to correlate cause and effect. Computational tools would then be utilized to translate data points into algorithms which may predict responsiveness to a diet.

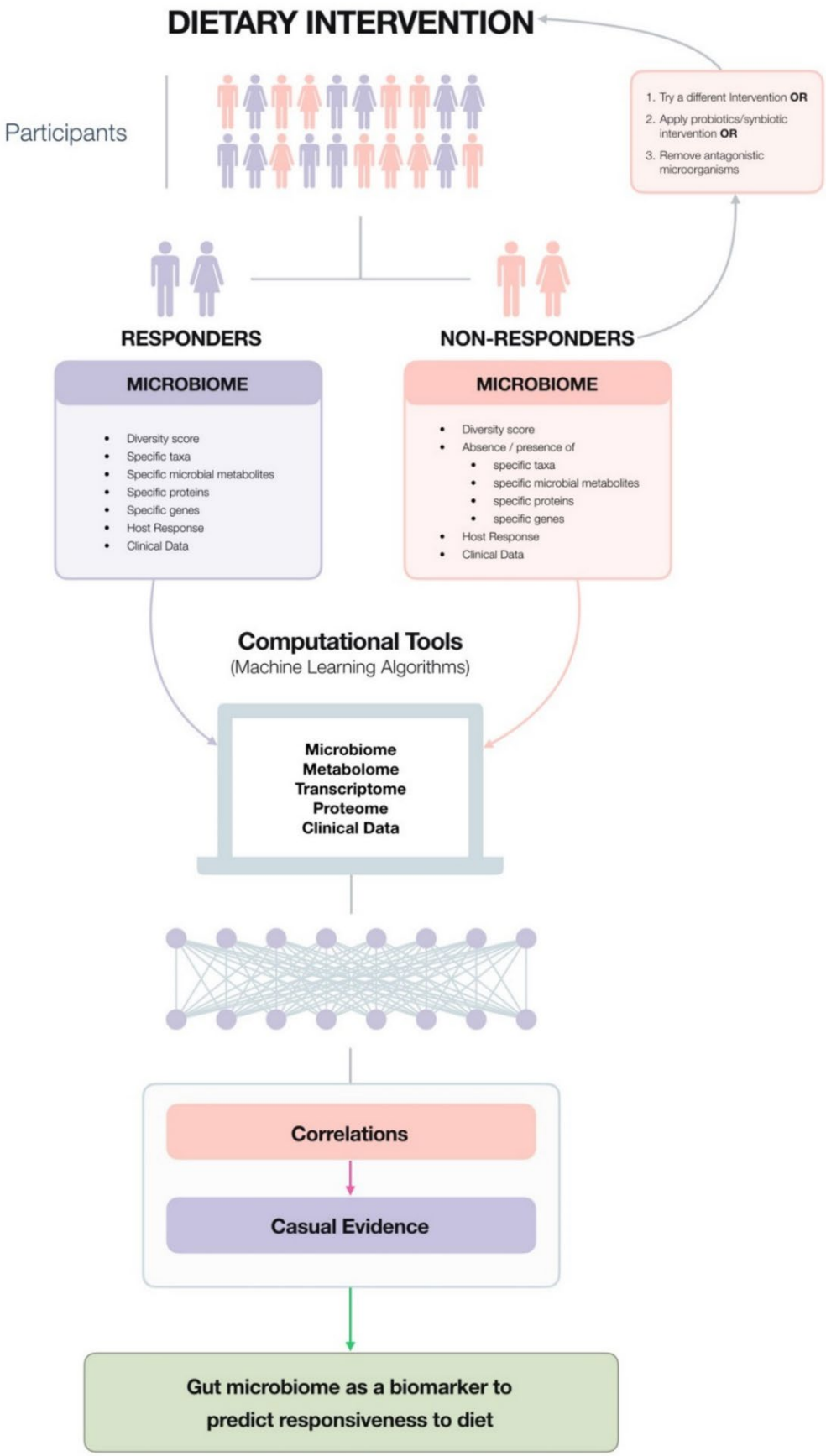

DIETARY INTERVENTION
Participants
1. Try a different Intervention OR
2. Apply probiotics/synbiotic intervention OR
3. Remove antagonistic microorganisms
RESPONDERS
NON-RESPONDERS
MICROBIOME
Diversity score
Specific taxa
Specific microbial metabolites
Specific proteins
Specific genes
Host Response
Clinical Data
MICROBIOME
Diversity score
Absence / presence of
specific taxa
specific microbial metabolites
specific proteins
specific genes
Host Response
Clinical Data
Computational Tools
(Machine Learning Algorithms)
Microbiome
Metabolome
Transcriptome
Proteome
Clinical Data
Correlations
Casual Evidence
Gut microbiome as a biomarker to predict responsiveness to diet

Figure 3.2 Microbiome data modeling for precision nutrition; from Mills et al. 2019.

Challenges and Special Considerations for Precision Nutrition

Precision nutrition is not universally adopted because of a myriad of challenges including financial, ethical, and logistical--not to mention scientific. There is a lack of well-designed clinical trials showing consistent results, and expensive technologies are required to collect and study an individual's DNA, gut microbiome, and response to food intake. The ethical and legal aspects of implementing precision nutrition should also be considered, including protecting consumer privacy in the use of precision nutrition technologies and tests. Further, if personalized approaches are accessible to only a small segment of the population this can further widen health disparities.

The path forward for precision nutrition must integrate diverse disciplines in an intentional manner that will be usable and applicable for a diverse cohort of patients, even though each of these patients will have unique and distinct recommendations. The International Society of Nutrigenetics/Nutrigenomics identifies the following items as imminent and future challenges to the field of precision nutrition.

Table 3.5 Imminent and future challenges for precision nutrition
Strengthening precision nutrition science
Creation of risk map
Creation of a reliable "bank" of polymorphisms
Tests of epigenetic assessment
Identifying valid biomarkers
Microbiome, lipidomic, proteomic studies
Implementation of public health policies
Development of innovative technologies for analyzing, synthesizing, integrating data
Applicability and integration with clinical practice
Tools for evaluating diet
Regulation of ethical and legal aspects
Cost reduction
Training personnel and improving knowledge delivery
Increase availability of trained allied health professionals capable of interpreting genetic data
Increase involvement of dietetic professionals in dietary recommendations
Promote introduction of nutrigenomic education into the curricula of allied health professionals and within medical curricula
Public education
Communication with and involvement of science writers
Dissemination of "lay" information via mainstream media in the form of print, screen, and social media

Precision Nutrition & Advanced Culinary Medicine E-Book

Module 4

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Chapter 4/Module 4: Table of Contents

Content	Resources

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	Personalized Nutrition As Medical Therapy for High-Risk Diseases, edited by Nilanjana Maulik, Taylor & Francis Group, 2020. *ProQuest Ebook Central*, http://ebookcentral.proquest.com/lib/kentucky-ebooks/detail.action?docID=6182012
	
	Guembe, M.J., Fernandez-Lazaro, C.I., Sayon-Orea, C. *et al.* Risk for cardiovascular disease associated with metabolic syndrome and its components: a 13-year prospective study in the RIVANA cohort. *Cardiovasc Diabetol* **19,** 195 (2020). https://doi.org/10.1186/s12933-020-01166-6
	
	Anderson, J.J.B., & Sparling, M.C. (2014). The Mediterranean Way of Eating: Evidence for Chronic Disease Prevention and Weight Management (1st ed.). CRC Press. https://doi.org/10.1201/b17032
	
	Castro-Barquero S, Ruiz-León AM, Sierra-Pérez M, Estruch R, Casas R. Dietary Strategies for Metabolic Syndrome: A Comprehensive Review. *Nutrients*. 2020; 12(10):2983. https://doi.org/10.3390/nu12102983
	
	Albosta, Michael, and Jesse Bakke. "Intermittent Fasting: Is There a Role in the Treatment of Diabetes? A Review of the Literature and Guide for Primary Care Physicians." Clinical diabetes and endocrinology 7.1 (2021): 3–3. Web. https://saalck-uky.primo.exlibrisgroup.com/permalink/01SAA_UKY/ija67f/cdi_doaj_primary_oai_doaj_org_article_4499d104150640e2984678a12ff6ae21
	
	Rynders, Corey A et al. "Effectiveness of Intermittent Fasting and Time-Restricted Feeding Compared to Continuous Energy Restriction for Weight Loss." Nutrients 11.10 (2019): 2442–. Web. https://saalck-uky.primo.exlibrisgroup.com/permalink/01SAA_UKY/ija67f/cdi_doaj_primary_oai_doaj_org_article_22ce3704c9594b878516e0e599575d14

Cardiovascular Disease (CVD) and Principles of Precision Nutrition

Cardiovascular disease (CVD) was the leading cause of death globally in 2017 and is associated with numerous risk factors including obesity/diabetes, metabolic dyslipidemia, hypertension, insulin resistance, lack of physical activity, smoking and alcohol consumption (Turner, Millns et al. 1998; Mackay and Mensah 2004). Many of these same risk factors comprise diagnosis of the Metabolic Syndrome (discussed later). It is estimated that nearly 18 million people died from CVD in 2015, equating to ~30% of all global deaths. CVDs are a group of disorders of the heart and blood vessels and include coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolisms (2017). In developed countries including North America, Europe, and Australia, at least one-third of all CVD is attributable to five lifestyle-modifiable risk factors: tobacco use, alcohol use, high blood pressure (BP), high cholesterol and obesity (Mackay and Mensah 2004). Precision Nutrition (PN) has been defined by Gibney and Goosens as an approach that assists individuals in achieving a lasting dietary behavior change that is beneficial for health (Gibney and Goosens 2016). According to these authors, there are at least three levels to PN (PN1– 3) increasing in complexity and individualization and, in turn, feasibility to implement (Gibney and Walsh 2013).

Precision Nutrition Level 1 - PN1 has seen widespread success using technology to record and analyze imputed food intake and physical activity levels and provide tailored advice to the end-user to improve health (Gibney and Walsh 2013). There is a multitude of software applications available that have transformed PN1 from an ideological concept that could only be accessed by those with the means, to widespread dissemination to anyone with access to mobile phone technology and an interest in PN for health. In terms of PN in the management of CVD, PN1 certainly provides a means to educate patients on implementation and adherence to a healthy diet, which is a critical lifestyle-modifiable factor that can profoundly reduce CVD risk.

Precision Nutrition Level 2 - PN2 involves tailoring nutritional advice based on a person's phenotype/metabotype. In the management of CVD, nutrition can and should be tailored to manage nutrient-modifiable risk factors such as weight, blood pressure, sodium intake and lipoprotein profiles as appropriate to the individual. There is growing interest in the use of dried blood spots (DBS) in PN2 to derive biochemical/metabolic profiles of individuals and adapt a diet according to these parameters (Celis Morales, Livingstone et al. 2015). The feasibility of using DBS in a large population, using blood samples taken remotely, to direct PN has recently been established in the European Union Seventh Framework Programme integrated project, Food4Me (Celis-Morales, Livingstone et al. 2015). This study analyzed a wide variety of biochemical measurements from DBS including glucose, total cholesterol, carotenoids, omega-3 (n-3) fatty acid index, fatty acids, and vitamin D (Celis-Morales, Livingstone et al. 2015). DBS can also be used for lipidomic (Gao, McDaniel et al. 2017), metabolomic (Wang, Sun et al. 2016) and proteomic (Martin, Bunch et al. 2013) analyses and thus a vast amount of data can be derived from a small sample size. Indeed, the expansive information that is acquired from DBS, using more sensitive analytical platforms, provides the power to group individuals into metabotypes wherein individuals are grouped into clusters with similar metabolic profiles (Gibney and Goosens 2016). Metabotype subgroups may respond differently to nutrients contributing to interindividual variability that exists during nutrition interventions. A recent study, for example, hypothesized that the interindividual variability to the lipid lowering properties of pomegranate may be due to variability in polyphenol metabolism (Gonzalez-Sarrias, Garcia-Villalba et al. 2017). Participants were grouped according to the microbially derived

ellagitannin-metabolizing phenotypes including urolithin metabotypes A, B and 0 (UM-A, UM-B and UM-0). The UM-B cluster exhibited the greatest CVD risk at baseline but also exhibited the greatest lipid-lowering response to phenolics (Gonzalez-Sarrias, Garcia-Villalba et al. 2017). This is a prime example of how PN may be implemented to prescribe the right diet to the right responder and move away from a one-size-fits-all approach to nutrition.

Precision Nutrition Level 3 - PN3 involves tailoring nutritional advice to a person's genotype. This is the premium level for PN and the most challenging to implement. In the era of genome-wide association studies (GWAS) and post-the Human Genome Project, it has been widely envisioned that both personalized medicine and PN would be based on the ultimate blueprint of a person, their genetic code (Gibney and Walsh 2013). One of the first single nucleotide polymorphisms (SNPs) to be identified that contributes to dysbetalipoproteinemia was in the Apolipoprotein (Apo) E gene which resulted in accumulation of triglyceride (TG)-rich lipoproteins in circulation (Utermann, Hees et al. 1977). There are three common isoforms of ApoE (ApoE2, ApoE3 and ApoE4) that are encoded by a gene on chromosome 19— 55– 60% of individuals are homozygous for the E3 allele (Davignon, Gregg et al. 1988; Minihane, Khan et al. 2000). Individuals carrying the ApoE4 allele have the highest levels of low-density lipoprotein (LDL)-cholesterol and ApoB, intermediate levels are observed in individuals homozygous for ApoE3, and the lowest levels are evident in those with the ApoE2 allele (Davignon, Gregg et al. 1988). Individuals with the ApoE2 allele also display reduced postprandial TG response to fish-oil intervention relative to non-E2 carriers, indicative of better response to fish-oils in individuals with this genotype (Minihane, Khan et al. 2000). This is one example of how dietary advice could be tailored to genotype. Those individuals with the ApoE2 allele should be encouraged to consume fish-oil enriched diets due to their propensity to yield beneficial effects from these nutrients.

Metabolic Syndrome

Excerpts adapted from:

- *Personalized Nutrition As Medical Therapy for High-Risk Diseases*, edited by Nilanjana Maulik, Taylor & Francis Group, 2020. *ProQuest Ebook Central*, http://ebookcentral.proquest.com/lib/kentucky-ebooks/detail.action?docID=6182012
- Guembe, M.J., Fernandez-Lazaro, C.I., Sayon-Orea, C. *et al.* Risk for cardiovascular disease associated with metabolic syndrome and its components: a 13-year prospective study in the RIVANA cohort. *Cardiovasc Diabetol* **19,** 195 (2020). https://doi.org/10.1186/s12933-020-01166-6
- Anderson, J.J.B., & Sparling, M.C. (2014). The Mediterranean Way of Eating: Evidence for Chronic Disease Prevention and Weight Management (1st ed.). CRC Press. https://doi.org/10.1201/b17032

The Metabolic Syndrome (MetS) refers to a constellation of interrelated risk factors that place an individual at high risk of developing CVD and type II diabetes. MetS is defined as a clustering of metabolic risk factors; a diagnosis is generally made when 3 or more of the following criteria are met (Anderson, Sparling 2014):

1. Abdominal obesity: waist circumference of at least 40 inches in men or 35 inches in women
2. Hypertriglyceridemia: triglyceride level of at least 150 mg/dL
3. Low HDL cholesterol: less than 40 mg/DL in men or less than 50 mg/dL in women
4. Hypertension: defined by systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg
5. Hyperglycemia: fasting blood glucose level of at least 100 mg per dL.

As mentioned above, a diagnosis of MetS is associated with elevated risk for developing cardiovascular diseases. In fact, individuals diagnosed with MetS have a 2-fold increased risk of CVD, mortality due to CVD, and stroke, and a 1.5-fold increased risk of all-cause mortality associated with MetS (Guembe, 2020).

The precise mechanisms underlying complex pathways of MetS are under investigation; however, it is understood that one's dietary patterns can contribute to the development of MetS. Weight gain and obesity, particularly elevated levels of visceral adiposity, contribute to hyperglycemia and hypertension (Maulik). Since a singular dietary recommendation and/or regimen can yield different outcomes from person to person, it would be helpful for practitioners to predict which dietary pattern could be most helpful for any patient (in other words, to utilize personalized or precision nutrition).

GENETICS & METABOLIC SYNDROME

The intricate link between multiple lifestyle-associated risk factors and cardiovascular disease (CVD) indicates the importance of maintaining a healthy diet for CVD management; but there is also an irrefutable genetic component to CVD (Khera and Kathiresan 2017). Clinical observation from the 1950s have supported the opinion that CVD is heritable (Gertler, Garn et al. 1951). A study of ~20,000 twins in Sweden confirmed this and showed increased CVD risk for those with close relatives affected by the disease and estimated that heritable factors account for 30– 60% of the interindividual variation in CVD risk (Marenberg, Risch et al. 1994; Zdravkovic, Wienke et al. 2002). The Framingham Heart Study similarly showed that having a parent or sibling with CVD was a strong predictor of the incidence of disease (Lloyd-Jones, Nam et al. 2004; Murabito, Nam et al. 2004). However, at the time of this resource publication, it is poorly understood whether poor lifestyle further exacerbates CVD in high-risk individuals. In updated genome-wide association studies (GWAS), it is estimated that heritability of CVD is 40– 50% (Won,

Natarajan et al. 2015). Many researchers once assumed that genetic predisposition is deterministic (White 1957), but in fact an individual's risk of developing CVD is a dynamic interplay between genetic and lifestyle factors (Khera, Emdin et al. 2016). Thus, lifestyle may accentuate genetic susceptibility, or not.

A cornerstone study by Khera et al. investigated to what extent increased genetic risk can be offset by healthy lifestyle (Khera, Emdin et al. 2016). The study involved over 55,000 participants across 3 prospective cohorts where adherence to healthy lifestyle was determined by using a scoring system consisting of 4 factors: 1. no smoking, 2. no obesity (BMI < 30), 3. physical activity at least once weekly and 4. consumption of a healthy diet. The polygenic risk score was derived from analysis of 50 SNPs that achieved genome-wide significance for association with CVD (Consortium, Deloukas et al. 2013). A healthy diet pattern was determined based on adherence to at least half of the following items (Mozaffarian 2016); high consumption of fruits, nuts, vegetables, whole grains, fish and dairy products and low intake of refined carbohydrates, processed meats.

PROOF OF CONCEPT FROM LIPGENE

There is major potential for nutrition research and primary care to use genome-wide association study (GWAS) data for more in-depth PN approaches to treat CVD; however, there are multiple hurdles that must be overcome to translate this into a clinical reality. A greater understanding of potential gene-nutrient interactions on newly identified SNPs is essential to implement PN3, and therefore much research is required in this field. Gene-nutrient interactions and implications for CVD have been comprehensively reviewed by Corella et al. (Corella, Coltell et al. 2017). A proof-of-concept study that has explored diet-nutrient interactions in patients with the metabolic syndrome was the pan-European LIPGENE study. LIPGENE was a multicenter, single-blind, randomized controlled trial that aimed to 1) determine the effect of reducing saturated fatty acid (SFA) consumption by altering quality of dietary fat and reducing quantity of dietary fat on the metabolic syndrome and its associated risk factors; and 2) determine if common genetic polymorphisms affect an individual's responsiveness to dietary therapy. The study included eight European centers and nearly 500 volunteers who were diagnosed with the metabolic syndrome; they were assigned to one of four dietary interventions:

1) high-fat (38% energy) SFA-rich diet
2) high-fat (38% energy) mono-unsaturated fatty acid (MUFA)-rich diet
3) isocaloric low-fat (28% energy), high complex carbohydrate diet
4) isocaloric low-fat (28% energy), high complex carbohydrate diet with 1g/d LC n-3 PUFA for 12 weeks (Shaw, Tierney et al. 2009; Tierney, McMonagle et al. 2011).

LIPGENE attempted to use genotype information of individuals to investigate responsiveness of singular SNPs to dietary fat on markers of the metabolic syndrome. For example, individuals with the minor allele at rs1799983 in the nitric oxide synthase 3 (NOS3) gene were shown to have a greater TG-lowering response to n-3 PUFA than major allele carriers (Ferguson, Phillips et al. 2010). Individuals with this genotype in turn were projected to yield the greatest benefit from increasing PUFA intake. By contrast, individuals with the minor alleles of rs266729 and rs10920533 SNPs in ADIPOQ and in ADIPOR1 were particularly sensitive to insulin resistance in response to SFA consumption (Ferguson, Phillips et al. 2010). It was therefore speculated that individuals carrying these minor alleles would be particularly responsive to SFA lowering to improve insulin sensitivity. These findings are excellent proof of concept of how PN3

might be realized. However, a lot of SNPs studied in previous nutrigenomic studies have not been validated in recent GWAS for CVD and go beyond the scope of this eBook.

Implementation of PN1 for the management of CVD depends on understanding of the optimal diet for the management of CVD. The current recommended dietary guidelines for CVD management include consuming a diet rich in fruits and vegetables, grains, low-fat or non-fat dairy products, fish, legumes, poultry, and lean meats (Krauss, Eckel et al. 2000; Eckel, Jakicic et al. 2014). In turn, recommendations are sub-divided into guidelines for body weight (match energy intake to energy needs), cholesterol profiles (limit foods high in saturated fat and cholesterol; and substitute unsaturated fats from vegetables, fish, legumes, and nuts), and blood-pressure management (limit salt and alcohol, maintain a healthy body weight, increase intake of vegetables, fruits, and low-fat/non-fat dairy products). Dietary patterns with an evidence base demonstrating efficacy toward the prevention, mitigation, or treatment of MetS included within this text are DASH (Dietary Approaches to Stop Hypertension), the Mediterranean Diet, and Intermittent Fasting.

Dietary Patterns

a. Dietary Approaches to Stop Hypertension (DASH)

Excerpts adapted from:

- Castro-Barquero S, Ruiz-León AM, Sierra-Pérez M, Estruch R, Casas R. Dietary Strategies for Metabolic Syndrome: A Comprehensive Review. *Nutrients*. 2020; 12(10):2983. https://doi.org/10.3390/nu12102983

In 1997, the Dietary Approaches to Stop Hypertension (DASH) diet became a promising strategy for the treatment of high blood pressure, and subsequent randomized clinical trials (RCTs) have supported this evidence. This eating pattern promotes vegetables, fruits, whole grains, low- or free-fat dairy products, legumes, and nuts intake, while restricting the intake of red and processed meat and sugar-sweetened beverages. The DASH diet is characterized by a low-fat content (27% of daily calorie intake from fat), especially saturated fats (6% of energy or less) and dietary cholesterol (150 mg per day or less, approximately), and reduced sodium content (from 1500 to 2300 mg/day), but it is rich in fiber (>30 g/day), potassium, magnesium, and calcium compared to other dietary patterns. The DASH diet has proven to be a useful strategy for the treatment of hypertension, and several epidemiological studies have associated higher adherence to the DASH diet with a better cardiometabolic profile. In a meta-analysis of several cohort studies, Schwingshackl et al. reported that higher adherence to the DASH diet was associated with a significant reduction in the risk of all-cause mortality, the incidence of or mortality by CVD and cancer, and the incidence of Type 2 Diabetes Mellitus (T2DM).

Epidemiological evidence suggests an association between higher adherence to the DASH diet and a better cardiometabolic profile and reduced risk of CVD. Increased adherence to the DASH diet was associated with 48% less risk of developing MetS. In contrast, body mass index (BMI), waist circumference, pro-inflammatory markers, and adiposity measures were significantly lower compared to individuals with lower adherence to the diet.

The DASH diet is highly nutritious, with a stress on consumption of vegetables and fruits, which translate into higher potassium, magnesium, and fiber intake – all which have shown a role in BP control, glucose metabolism, and insulin response. Moreover, limiting sodium and fat – chiefly saturated fat – is a double benefit. Research demonstrates that patients who are committed to adherence will benefit from reduced risk for CVD.

Figure 4.1. The DASH dietary pattern emphasizes vegetables, fruits, and whole grains with limits on sodium, sweets, and meats (even lean cuts).

b. Mediterranean diet approach (Almudena Sanchez-Villegas)

The Mediterranean diet is a well-known and recognized dietary pattern. There is substantial scientific evidence backing the efficacy of the Mediterranean diet to reduce risk for various chronic diseases, including hypercholesterolemia, hypertension, and insulin resistance--all facets of the MetS. Multiple observational studies and clinical trials have demonstrated favorable outcomes associated with adopting the Mediterranean diet. A few examples of evidence along these lines include:

- **The SUN (Seguimiento Universidad de Navarra) study.** A Spanish prospective cohort study based on university graduates that followed 3,609 participants (initially free of cardiovascular disease) for 4.9 years. Participants of the SUN study with the highest adherence to the Mediterranean Diet (a score >6, as measured by the Mediterranean Diet Score, or MDS) exhibited a lower cardiovascular risk (significant risk reduction = 59%) compared to those with the lowest adherence score (<3). For each 2-point increment in the score, the adjusted relative reduction in risk was 20% for total cardiovascular disease and 26% for coronary artery disease (CAD).

- **The EPIC study (European Prospective Investigation into Cancer and Nutrition)** is one of the largest cohort studies in the world, with more than 500,000 participants recruited across 10 countries and followed for 15 years. This study sought to determine the relation between Mediterranean Diet adherence and risk of incident coronary heart disease events in the five Spanish centers of the EPIC study. After following up to 41,078 participants for about 10 years, the researchers found that high compared with low relative Mediterranean Diet adherence was associated with a significant reduction in coronary heart disease risk (relative risk reduction of 40%, 95% confidence interval = 23-53%). A 1-unit increase in relative Mediterranean Diet score was associated with a significant reduction in the risk (6%). In other words, for both the SUN and EPIC studies, the more closely that participants followed the Mediterranean diet, the lower their relative risk for developing cardiovascular disease.
-
- A landmark trial that examined the efficacy of two variations of the Mediterranean diet is **the PREDIMED trial.** PREDIMED trial was a parallel-group, multicenter, randomized trial that compared the outcomes of adhering to a Mediterranean diet supplemented with extra-virgin olive oil (EVOO) versus a Mediterranean diet supplemented with nuts, versus a control diet (the group was advised to lower dietary fat). There was almost a 5-year follow-up with this trial, but it ended earlier than planned due to interim analysis. The data indicated that the control group participants were experiencing a significantly higher frequency of CVD events and CVD-associated mortality compared to the two diet groups who were consuming the Mediterranean diet (regardless of whether it was supplemented with mixed nuts or extra virgin olive oil).

Mediterranean patterns of eating are representative of the most beneficial diets known to humankind. Because they included so many plant foods, including fruits, vegetables, legumes, whole grains, nuts, and seeds, they historically provided just enough calories each day to meet the needs of energy expenditure in daily activities. The major benefit in terms of calories was that individuals did not become obese, as occurs so frequently now in the United States and many other nations. So, calorie control was built into the typical eating pattern with little other constraint on food intake needed.

Adherence to a Mediterranean dietary pattern has been demonstrated to improve health and reduce mortality from many chronic diseases, especially cardiovascular diseases, type 2 diabetes mellitus, and diet-related cancers. Chronic disease rates are generally lower in Mediterranean populations than in other Western nations (Anderson, Sparling 2014 “The Med Way of Eating”).

Are there aspects of the Med Diet that work for some, but not others? What elements need evaluation with a precision nutrition lens? How can we tweak this diet for each patient cohort? These are some of the questions to consider regarding positioning of the Mediterranean diet within precision medicine.

Table 4.1 Common foods within the traditional diet of Mediterranean countries (Almudena Sanchez-Villegas)

Foods	Description
Veg & fruits	Vegetables and fruits are important sources of minerals, vitamins, antioxidants, and fiber. Benefits of their consumption are amplified if they are cooked or dressed with olive oil.
Grains	The nutritional composition of grains may vary depending on the variety and environmental growing conditions. In general, cereal grains are high in carbohydrates, low in fat, good sources of protein and provide varying amounts of fiber, vitamins, and minerals. Cereal products should contain whole grains, including wheat, oats, rice, rye, barley, and corn. Grains should also be consumed in minimally processed forms.
Olives and olive oil	Olive oil is a central component in the cuisine of the countries surrounding the Mediterranean Sea. This type of vegetable oil has a peculiar fatty acid composition (with a large proportion of monounsaturated fat—mainly oleic acid—and a relatively low proportion of saturated fat) and contains other minor compounds (tocopherols and carotenoids among others) with antioxidant properties. Olive oil is the principal source of dietary fat in the Mediterranean Diet and is frequently used to dress salads and vegetables, and in cooking or baking. The variety “extra-virgin” olive oil is highest in health promoting fats, phytonutrients, and other important micronutrients.
Nuts, legumes, seeds	Nuts, legumes, and seeds are packed with vitamins and minerals. Nuts and seeds also provide healthy mono- and polyunsaturated plant oils as well as protein. Legumes, which include beans, are filling and contain lean protein.
Fish and shellfish	Fish and shellfish are preferred over meat in the traditional Mediterranean diet, although the quantity of fish consumed varies widely between and within Mediterranean countries. Fish and shellfish are an important source of healthy protein and essential heart-healthy omega-3 fatty acids.
Cheese and yogurt	Dairy products from a variety of animals including goats and sheep, principally in the form of yogurt and cheese, are consumed in low to moderate amounts.
Meat	Consumption of red meat and processed meats is lower in the Mediterranean population than the consumption of white meat.
Wine	Moderate wine drinking in the context of the meals has been a long-standing tradition in the Mediterranean basin, except for Islamic populations of this area. “Moderate” generally refers to one glass per day for women, and two glasses for men.
Herbs and spices	Herbs and spices add flavors and aromas to foods, reducing at the same time the need to add salt or fat when cooking. Herbs and spices are very common in Mediterranean cuisine; they contain several health-promoting antioxidants and contribute to the differences between the broad varieties of culinary cultures.

c. Intermittent Fasting, Weight Management & Metabolic Syndrome

Excerpts adapted from:

- Albosta, Michael, and Jesse Bakke. "Intermittent Fasting: Is There a Role in the Treatment of Diabetes? A Review of the Literature and Guide for Primary Care Physicians." Clinical diabetes and endocrinology 7.1 (2021): 3–3. Web: https://saalck-uky.primo.exlibrisgroup.com/permalink/01SAA_UKY/ija67f/cdi_doaj_primary_oai_doaj_org_article_4499d104150640e2984678a12ff6ae21

INTERMITTENT FASTING

Intermittent fasting has recently gained popularity as a means of improving body composition and metabolic health [28, 29]. Intermittent fasting (IF) refers to eating patterns based around the principle of consuming very little to no calories for time periods ranging from 12 hours to several days with a regular and consistent pattern [28]. With IF, more emphasis is placed on **when** eating takes place, as opposed to **what** is eaten at any given time. There are several different types of IF in theory and practice. One such regimen is alternate day fasting, in which days of fasting are separated by days of ad libitum feeding [29]. Another method is periodic fasting, in which individuals fast for 1 or 2 days a week (also referred to as 5:2 or 6:1 fasting) [29]. Finally, the most common method is time-restricted feeding (TRF), in which food consumption is only allowed during a specified window of time each day, typically with 16–20 h daily fasts [29].

It has long been known that restricting calories can lead to weight loss. A study by Larson-Meyer et al. [34] showed that 25% calorie reduction either via diet alone or diet in conjunction with exercise led to improvements in insulin sensitivity and reduction in β-cell sensitivity in overweight, glucose-tolerant individuals. However, several obesity trials have demonstrated that humans have significant difficulty sustaining daily calorie restriction for extended periods of time [28]. On the other hand, IF has higher compliance and has shown promise in the improvement of metabolic risk factors, body composition, and weight loss in obese individuals [28, 35, 36]. It has been shown that these beneficial effects are due in part to the shift during fasting from the utilization of glucose to fatty acids and ketones as the body's preferred fuel source [28]. During this transition the body begins to switch from the synthesis and storage of lipids to mobilization of fat in the form of ketone bodies and free fatty acids [28]. This transition of fuel source, or metabolic reprogramming, has been highlighted as a potential mechanism for many of IF's beneficial effects. Interestingly, the research studies examining IF have demonstrated multifarious health benefits outside of weight loss, such as improved sleep, decreased brain fog (improved cognition), improved insulin sensitivity, among others. Further, IF has been shown to reduce adiposity, particularly visceral fat, and truncal fat, largely due to mild energy deficits [12, 17]. It is through this reduction in adiposity that patients may experience improvements in their leptin/adiponectin levels and sensitivity, leading to improved appetite control and lower levels of chronic inflammation thus improving several risk factors for type 2 diabetes.

It is the development of insulin resistance, which is defined as the necessity of higher circulating insulin levels to produce a glucose lowering response, that is thought to be responsible for the development of type 2 diabetes [7]. To promote regulation of glucose homeostasis, insulin works primarily on receptors in skeletal muscle, liver, and white adipose tissue [7]. In short, there are several proposed mechanisms regarding the development of insulin resistance. One of the more prominent theories describes the

association of increased adiposity and the subsequent chronic inflammation that leads to the development of insulin resistance in tissues [7].

IF may reduce adiposity and subsequently insulin resistance via reduction of caloric intake as well as due to metabolic reprogramming. In addition, energy/nutrient depletion (such as that achieved through reduced caloric intake) has been shown to promote healthier aging and reduction in chronic disease through increased activation of AMP activated protein kinase (AMPK) [37]. AMPK responds both to increased AMP/ADP:ATP ratios as well as to endocrine signals of hunger and satiety [37]. The role of AMPK at a biochemical level is outside of the scope of this review; however, activation of AMPK through a low energy state has been shown to initiate physiologic responses that promote healthy aging [37]. Increased levels of insulin, whether through increased energy intake or insulin resistance, leads to the activation of downstream mediators that ultimately inhibit AMPK. The role of AMPK in improved insulin sensitivity is most evident via the positive effects of the commonly prescribed biguanide, metformin. Metformin is known to promote the activation of AMPK and has been shown to be very effective in the treatment of type 2 diabetes as well as in the mitigation of several chronic disease states [37]. In theory, decreased energy intake, such as that achieved through intermittent fasting, will lead to prolonged decreased levels of insulin production and increased levels of AMPK, which likely plays a role in the improvements in insulin sensitivity and glucose homeostasis.

INTERMITTENT FASTING AS A TREATMENT OPTION FOR TYPE 2 DIABETES

Several studies have shown promise for the use of IF protocols as a potential treatment for diabetes. In a systematic review and meta-analysis by Cho et al. [32] that included studies evaluating patients both with and without pre-diabetes (diabetic patients were excluded), it was found that of 8 studies comparing the effects of an intermittent fasting diet to a control group, BMI decreased by 0.75 kg/m^2 over periods ranging from 4 to 24 weeks. Furthermore, of 8 studies comparing intermittent fasting to a control group in the evaluation of glycemic control, it was found that the intermittent fasting group had significant reductions in fasting glucose levels (− 4.16 mg/dL; $p = 0.003$). Lastly, when comparing leptin and adiponectin levels between the intermittent fasting subjects and the control subjects in all studies, the reviewers found increased adiponectin levels (1008.87 ng/mL; $p = 0.023$) and decreased leptin (− 0.51 ng/mL; $p < 0.001$) [32]. A case series by Furmli et al. [26] followed three patients with type 2 diabetes over several months after beginning an intermittent fasting regimen consisting of three, 24 h fasts per week. Over the course of the study, all patients had significant reductions in HbA1C, weight loss, and all the patients were able to stop their insulin therapy within 1 month [26]. Interestingly, the three patients in this case series all reported tolerating fasting very well, and no patient stopped the intervention at any point out of choice [26]. This suggests that intermittent fasting may not only be successful as a non-medicinal treatment option for patients with type 2 diabetes but supports the notion that this intervention is tolerable as well. Carter et al. [19] performed a clinical trial in which 137 adults with type 2 diabetes were divided into two groups, one intermittent energy restriction group (500–600 kcal/day for 2 days per week and normal diet every other day) and a continuous energy restriction group (1200–1500 kcal/day). After 12 months of intervention, the two groups showed similar reductions in HbA1C levels and greater reductions in weight in the intermittent energy restriction group. Finally, a similar clinical trial by Gabel et al. [16] compared an alternate day fasting regimen (25% of energy needs on fasting days, 125% of energy needs on non-fasting days) to continuous energy restriction (75% of energy needs daily) and a control group of obese, non-diabetic patients. Over an intervention period of 12 months, there were similar reductions in body weight, BMI, and fat mass between the alternate day

fasting and continuous energy restriction groups, however there were significant reductions in fasting insulin levels (− 44%; $p < 0.05$) and homeostatic model assessment of insulin resistance (HOMA-IR) levels (− 53%; $p < 0.05$) in the alternate day fasting group [16]. HOMA-IR is a marker used to measure levels of insulin resistance.

PRESCRIBING INTERMITTENT FASTING IN PRACTICE: RECOMMENDATIONS

While alternate day fasting and periodic fasting have demonstrated efficacy in improving metabolic risk factors, it may be difficult to convince patients to give up or severely restrict calories for an entire 24 h period. In America, we often eat 3 meals per day in addition to frequent snacking. Furthermore, in American culture most social engagements involve food. Asking patients to eliminate these experiences from their day-to-day lives may become burdensome, and thus hinder patient compliance. Finally, patients switching to an intermittent fasting regimen may initially experience symptoms such as hunger and irritability, although these symptoms often dissipate within the first 30 days [38]. Therefore, it would be more appropriate to gradually introduce intermittent fasting in the form of time restricted feeding. For example, clinicians may first recommend that patients restrict their intake to a daily 12 h period, typically an overnight fast (for example, 7 pm to 7 am). As patients become more comfortable with this pattern of eating, the feeding window can be restricted further (16 h fast followed by an 8 h feed or 20 h fast followed by a 4 h feed). This allows the patient some daily flexibility in choosing when to consume calories, thus increasing the likelihood of compliance. Lastly, patients who have become adapted to time restricted feeding may choose to switch to alternate day or periodic fasting with the supervision and guidance of a registered dietician. See Fig. 5 for a detailed example of an intermittent fasting prescription.

PRESCRIBING INTERMITTENT FASTING IN PRACTICE: CONSIDERATIONS

When considering the use of fasting in patients with diabetes, several points should be weighed. First, it is important to discuss potential safety risks associated with fasting. Patients taking insulin or sulfonylurea medications should be closely monitored by their healthcare provider to prevent hypoglycemic events [39]. Because studies are demonstrating a decreased need for insulin in patients who follow IF protocols, blood glucose levels and medication titration should be observed closely by the physician. Physicians should help patients make appropriate adjustments to their medications, especially on days of fasting. Physicians may choose to have patients keep daily blood sugar and weight logs and send them weekly or biweekly via electronic message to assist providers in medication titration over time. Of note, while the goal of adapting this pattern of eating is to reduce or eliminate the need for medications, including insulin, there are situations in which insulin may be necessary, such as severe hyperglycemia. Failure to do so may result in significant consequences, such as the development of hyperosmolar hyperglycemic syndrome. Additional concerns, although unlikely, include vitamin and mineral deficiencies and protein malnutrition [39]. Patients should be educated regarding the importance of consuming nutrient-rich meals and adequate protein intake during feeding periods. Furthermore, it may be important to consider vitamin or mineral supplementation depending on the patient's dietary practices and the desired length of a fasting regimen. Patients should also be counseled on the need for adequate hydration during periods of fasting, as they will be required to replace fluids that might normally be consumed through food in addition to regular daily requirements. As many physicians may not be trained extensively in nutritional sciences, and further, may not have time to follow daily with patients to ensure appropriate nutritional intake, consultation with a registered dietitian is highly recommended. Lastly, it is important to consider populations in whom fasting may not be appropriate. These include pregnant/lactating women, adults of

advanced age, individuals with immunodeficiencies, individuals with hypoglycemic events, and patients who suffer from eating disorders [39].

Precision Nutrition & Advanced Culinary Medicine E-Book

Module 5 – Neurological and Mental Health Disorders

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Introduction

In a pandemic and post-pandemic era, the spotlight on mental health and decreasing existing stigmas about mental health has been at an all-time brightness. Any role for nutrition and food within neurological and mental health management can be a heavy and controversial topic, especially depending on who is a part of the conversation. Research is ongoing in this field, but much groundwork has been established at the time this chapter was written and compiled.

For example, studies have shown that individuals who consume higher quality diets are at reduced risk for incidence of depression. The key point here being reduced risk, not to be protected from. Further, specific medical and prescriptive diets have been shown clearly to be efficacious for extremely specific mental health conditions, such as epilepsy. The ketogenic diet and research supporting its use in intractable epilepsy are discussed here. Dementia and Alzheimer's Disease are increasing in case numbers and concern as an aging population grows older, lives longer, and becomes at increased risk of developing either. These patients can suffer with dysphagia, which is a risk for malnutrition. Information describing evidence-based dietary approaches for this population are also discussed.

Depression

Adapted from Owens, et al.

The **etiology of depression** is complex and not yet fully understood but is thought to involve cognitive (Watkins 2008; Gotlib & Joormann 2010), genetic (Mullins & Lewis 2017), and environmental (LeMoultet 2020) factors, as well as physiological factors such as hormones (Owenset al. 2014), inflammatory markers (Lamerset 2019), and arousal and wakefulness regulation (Hegerl & Hensch 2014; Jawinskiet 2019). **Lifestyle factors** are also thought to play a role, including most notably sleep, exercise, and diet (Lopresti, Hood & Drummond 2013). The relationship between diet, nutrition, and mood is complex and likely to involve interactions and reciprocal relationships. For example, it is suggested that stress and depression can shape gut microbiota, which in turn may affect stress and depression (Madison & Kiecolt-Glaser 2019). More on the gut-brain axis and role of gut microbiota in the "Gut Brain Axis" section, below. It is also increasingly recognized that modern lifestyles may lead to unhealthy diets, which may in turn contribute to both an obesogenic (Garcıa, Long & Rosado 2009; Bl€uher 2019) and "depressogenic" social environment (Hidaka 2012). The obesity global pandemic (Abarca-Gomezet al. 2017) could be linked to depression as the two factors often co-occur (Sutariaet al. 2019). In fact, researchers have noted that obesity and depression may have a bi-directional relationship where increase in one is associated with increase in the other over time (Luppinoet al. 2010; Marmorstein, Iacono & Legrand 2014). Furthermore, obesity and depression might share common biological mechanisms (Milaneschiet al. 2019), including, for example, inflammatory processes (Bellmore 2018).

One emerging approach to either the prevention or treatment of depression aims to improve diet and nutritional status. Under this framework, it is acknowledged that diet and nutritional status have an important yet complex relationship with mental health (Sanchez-Villegas & Martınez-Gonzalez 2013; Sarriset al. 2015; Jacka 2017; Lassaleet al. 2019). Theoretically, nutrients from diet or supplements can treat or prevent depression in two main ways: helping the brain to function well and providing neuroprotective effects. It has been shown, for example, that **omega-3 fatty acids** have pluripotent beneficial effects in the brain by upregulating adult neurogenesis (Beltzet al. 2007) and brain-derived neurotrophic factor (BDNF) protein expression (Wu, Ying& Gomez-Pinilla 2004; Raoet al. 2007), promoting metabolism, release, uptake, and receptor functions of key neurotransmitter systems (e.g. serotonin and dopamine) (Grossoet al. 2014a) and regulating stress via the Hypothalamic-Pituitary-Adrenal Axis (Thesinget al. 2018). **Neuroprotection from nutrients** may come in the form of anti-inflammatory processes (Wallet al. 2010), reducing apoptosis (Harmset al. 2011) and reducing oxidative stress (Limaet al. 2018). Research has assessed the links between specific nutrients and the prevention or treatment of depression. For example, dietary omega-3 is associated with a reduced risk of depression (Grossoet al. 2016), omega-3 supplementation versus placebo has demonstrated a beneficial effect on depressive symptoms (Liaoet al.2019), and vitamin D supplementation may benefit those with clinical depression (for a review on the connection between vitamin D and depression, see Parker, Brotchie & Graham 2017). However, it has also been argued that single nutrient supplementation is unlikely to be maximally effective, given that nutrients are not consumed in isolation (Opieet al. 2015).

*Whole-Diet Approaches (*Adapted from Owens, et al.)

A whole-diet approach is one that consists of eating predominantly or exclusively unprocessed or unrefined foods including grains, nuts, seeds, fruit, and vegetables. Research in this area focuses on high-quality diets that are nutrient dense and low in ultra-processed foods (e.g., the Mediterranean diet or traditional diet). There is robust observational evidence to suggest that such high-quality diets are at least associated with lower risk of depression (Molendijket al. 2018; Lassaleet al. 2019; Nicolaou, Colpo & Vermeulen 2019) and in addition, there is likely to be a complex bidirectional relationship between the two (Elstgeestet al. 2019). However, more work in this nascent field is needed to test the causal status of nutrients and diet quality and the prevention of depression; more randomized controlled nutritional intervention trials (RCTs) are required. Nevertheless, nutrition-based approaches are attractive candidates for mental health prevention strategies for several reasons, including the fact that they have the potential to reach many people and have additional wide-ranging positive health benefits: including promoting healthy immune function (Wintergerst, Maggini & Hornig 2007), and reducing negative effects of diabetes (Salas-Salvadoet al. 2015), heart disease (Grossoet al. 2017) and cancer (Auneet al. 2011). In addition, healthy diets can encourage healthy weight loss which may itself provide wide-ranging health benefits, potentially including preventing depression. Several studies have shown positive effects of behavioral weight control on both depressed mood and weight (e.g., Brinkworthet al.2009; Faulconbridgeet al. 2018) and as a result, nutritional interventions could also lead to health economic benefits (Gyleset al. 2012). The recently completed MooDFOOD intervention (Rocaet al. 2016; Botet al. 2019) is one such randomized controlled prevention trial that investigated the role of nutrition and nutrition-related psychological factors on depression. A recent meta-analysis of 16 randomized controlled trials (RCTs; the majority looking at non-clinical depression) suggests that a whole-diet approach may provide a small but significant benefit to reduce symptoms of depression. Examples include:

- A trial that was excluded from the review cited above is the SMILES trial (Jacka et al. 2017) which involved subjects diagnosed with clinical depression and reports significant differences in the reduction of depression symptoms for a dietary support group versus a social support group.
- HELFIMED trial (Parletta et al. 2019) was a whole-diet RCT for clinical depression that recruited patients through a general practitioner (GP). GP-reported or self-reported depression included subjects randomized to either a “MedDiet” group receiving nutrition education from dietitians and nutritionists who received baskets of Mediterranean-style foods and attended cooking workshops, and took fish oil supplements for 6 months, or a group who attended a social group every two weeks for 3 months. The results showed a statistically significant reduction in symptoms of depression for the MedDiet group, where 60% fewer participants experienced ‘extremely severe’ depression.
- An additional clinical trial with results forthcoming is the PREDI-DEP trial. This trial will investigate the effect of a dietitian-led Mediterranean-style diet supplemented with olive oil on the prevention or the recurrence of depressive disorder among participants with a history of clinical depression (Sanchez-Villegas et al. 2019).

Although there are still very few RCTs assessing integrative nutritional and psychological approaches to depression prevention, the current literature includes evidence, albeit limited, that nutritional supplements are not effective for the prevention of depression. It therefore remains an open question as to whether future nutrition-based interventions will have the ability to prevent depression. There is some evidence, on the other hand, for small beneficial effects of omega-3 supplements in the treatment of

depression as an adjunctive therapy. Whole-diet approaches may yield beneficial effects on depressive symptoms in clinical depression (see the SMILES trial; Jacka et al. 2017), although most studies have used non-clinical populations (Firth et al. 2019b). This latter fact leaves open the possibility that there is potential for depression prevention effects through whole diet approaches, but more research is needed in this area to ascertain this. Any recommendations for patients at risk or in treatment for depression should be carefully taken. Always **proceed with caution to ensure that we do not cause harm**, either directly through any iatrogenic effects (e.g., negative effects of supplements) or by inadvertently signposting those in need, whether they are patients with clinical depression or individuals with elevated symptoms or with known risk factors for disorder, to ineffective interventions, when they might otherwise seek help from interventions known to be efficacious.

Adapted from Ljungberg et al.

Conversely, research in this area has also examined the effect of a pro-inflammatory dietary pattern on risk for depression and indices for risk. A review published in the International Journal of Environmental Research and Public Health analyzed 22 research studies containing over 455,000 participant reports. All students included in their report had considered potential confounding factors, such as age, gender, marital status, education, income, occupation, physical activity, smoking, alcohol, and body mass index.

From their report:

> *Several studies showed an association between dietary intake with inflammatory potential and risk of depression in different populations [17,18,20,22,33]. Products associated with less impact on systemic inflammation have been found to be vegetables, whole grains, olive oil, and fish. Products such as sweets; refined flour; high-fat products; red and processed meat were associated with a greater impact on systemic inflammation [17]. The results showed that a pro-inflammatory diet was associated with a significantly increased risk of depression in the subgroup of women; middle-aged adults; and people with overweight and obesity. Thus, the relationship was strongest in people with overweight and obesity [17]. An increased risk of depression was associated with a high proportion of processed foods in the diet, and for each 10% increase of the proportion of processed foods [18]. High intake of pro-inflammatory food was associated with significantly increased risk of depressive symptoms [17,18,20,22]. In subgroups of men, smokers and physically inactive, a diet consisting of a higher proportion of pro-inflammatory foods, significantly increased the risk of depressive symptoms [20]. Associations between food with inflammatory effect and increased risk of depression were calculated with significance in a cross-sectional study performed in USA [22]. A high intake of inflammatory diet was significantly associated with the occurrence of frequent anxiety in the same study. In another study from USA, the results indicated a significant association between inflammatory diet and risk of depression in women [33].*

Epilepsy and Ketogenic Diet

Adapted from D'Andrea et al.

Epilepsy is a disabling and common neurological disease, which can be controlled successfully in most patients with one or more antiepileptic drugs. Approximately 30% of patients with epilepsy have refractory epilepsy, that is, have a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained relief of seizures (Picot et al., 2008; Kwan et al., 2009). Some of these patients are not surgery candidates, so it is necessary to search for alternative treatments for epilepsy, such as palliative surgery, neuromodulation, and a ketogenic diet (KD).

The **classic ketogenic diet (CKD)** is rich in lipids (90% calories from dietary fats) and protein, to produce ketosis, and simulates a state of starvation. It is a rigid diet, mathematically and individually calculated, and medically monitored. It must provide adequate vitamins and minerals. The CKD induces an effect like a fasting state physiologically, in doing so altering the metabolism to use fats as a primary fuel source; catabolism of fatty acids in the liver produces ketone bodies (KB) and the induction of urinary ketosis (Rho, 2017).

Recent studies have found a significantly positive outcome with the use of the KD for treatment of refractory epilepsy in children and adults (Barborka, 1928; Neal et al., 2008; Kverneland et al., 2015; Liu et al., 2018).

History of the classic ketogenic diet and therapeutic potential for epilepsy:

Two Parisian physicians, G. Guelpa and A. Marie, recorded the first modern use of starvation as a treatment for epilepsy in 1911 (Wheless, 2008). More modern use of this therapy began in the early 1920s (Lima et al., 2014; Yuen and Sander, 2014), when Drs. Stanley Cobb and W.G. Lennox at Harvard Medical School observed the effects of starvation as a treatment for epilepsy, noting that seizure improvement typically occurred after 2–3 days (Wheless, 2008). In the same period, Dr. Russel M. Wilder a physician at the Mayo Clinic in Minnesota, suggested that a specific diet could produce similar benefits to fasting, and proposed a diet that produced ketonemia. He studied a series of patients with epilepsy and demonstrated a result equivalent to fasting and that was maintained for a much longer period. This new concept of diet was designated the “KD”.

Adapted from Lambert et al.

Despite the efficacy of the ketogenic diet, most patients discontinue the diet. Reasons for decreasing diet adherence or discontinuing are due to the diet’s unpalatable and restrictive features. As a result, new variations of the classic ketogenic diet have emerged, and there are now five variations (also described in a video linked in Module 5):

1. the classical KD [1],
2. medium chain triglyceride KD (MCT KD) [2],
3. modified Atkins diet (MAD) [3],
4. low glycemic index treatment (LGIT) [4]
5. modified ketogenic diet (MKD) [5]

Several studies have shown that the new variants of the KD have some degree of efficacy to the CKD (Kossoff et al., 2006; Tonekaboni et al., 2010; Coppola et al., 2011; Miranda et al., 2012; El-Rashidy et al.,

2013). This indicates that variations of the KD can (at times) keep a patient in a state of ketosis. Knocking a previously ketogenic patient out of ketosis can cause epileptic seizures to return. Table 5.1 describes variations of the KD and their effect on seizure protection.

Modified Atkins Diet (MAD)	- 1:1 ratio of fat to carbohydrates to protein - Dietary fat is encouraged, and carbohydrates are limited to 10-20 g/day in children and 15-20 g/day in adults - Generally effective in children, lower carbohydrates very important in the first 3 months - Generally effective in adolescents and adults (higher adherence); proportion of patients showing >50% seizure control ranges from 20 to 70%
Low Glycemic Index (LGIT)	- 60% fats; 30% protein; 10% carbohydrates - Low glycemic index (GI) foods (GI < 50) - GI measures the tendency of a food to raise the blood glucose levels, compared to an equivalent amount of reference carbohydrate, usually glucose - Low # of high-quality studies - Proven effective in treatment of focal and generalized epilepsies

Table 5.1 Variations of the KD

As presently understood, the ketogenic diet is involved in multiple mechanisms responsible for biochemical alterations, including cellular substrates and mediators responsible for neuronal hyperexcitability. However, it is not yet known with certainty whether the success of the KD for refractory epilepsy is due to a single or several mechanisms (Bough and Rho, 2007; Lutas and Yellen, 2013; Rho, 2017; Youngson et al., 2017); in other words, no one can say with 100-percent certainty why it works – it just does! This is discussed further below.

KDs are the treatment of choice for certain neurometabolic disorders, such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency, and are an effective treatment option for drug-resistant epilepsy (DRE) [6,7]. KDs are a resource-intensive treatment, with a dietitian as an essential member of the multidisciplinary team (MDT) [6,8]. Regimens are demanding of the skill and expertise of the dietitian due to their inherent complexity, the need for individualized dietary calculation (to take into consideration clinical condition, age, feeding ability, nutritional requirements, educational status, and socio-economic circumstances), meal planning and recipe development, regular patient/caregiver contact, and liaison with other healthcare professionals. On-going follow-up is crucial to fine-tune the diet, manage any adverse side effects, and for its safe and successful discontinuation.

Although attrition from KDs occurs (due to poor diet tolerance or lack of efficacy) [7], and this will impact diet duration, recommendations are that KDs for DRE are discontinued if unsuccessful after a minimum of three months and after two years in patients where they have been efficacious [6]. However, there is no maximum duration for the use of KDs in DRE, and 30% of cases continue for longer or return to diet if seizures reoccur after weaning off [6,9].

Plausible Mechanisms for Efficacy of Ketogenic Diet to Effect Seizure Activity

- **Energy and Neuronal Metabolism**: In normal conditions, the energy substrate for neurons is glucose. To facilitate its diffusion through the blood-brain barrier, glucose transports are present in the brain capillary endothelial layer (Greene et al., 2003). The metabolism of glucose produces rapidly available energy that is necessary and utilized for seizure activity. However, in patients on the KD, the blood glucose energy levels are low, and the brain begins to use ketone bodies (acetoacetate, hydroxybutyrate) for energy. This anaerobic metabolism slows the energy availability, which reduces seizures. The anticonvulsant propriety of a decrease in glucose metabolism has been shown in experimental models in which the administration of 2-Deoxy-D-glucose elevates the seizure threshold (Garriga-Canut et al., 2006). The anticonvulsant effect of the KD can be quickly reversed after glucose infusion (Huttenlocher, 1976). Thus, the presence of ketone bodies and the reduction of glucose levels are both potential mechanisms underlying the anti-convulsive properties of the KD.
- **Synaptic Function**: Chronic ketosis elevates the brain energy reserve via stabilization and reduction of excitability of synapses (Devivo et al., 1978). The energy reserve is directly associated with mitochondria, which are important elements to consider in the antiepileptic effect of KD. Bough et al. (2006) demonstrated an increase in mitochondria biogenesis in an experimental model of rats fed with KD (Bough et al., 2006). The increase in mitochondrial metabolism leads to an increase in ATP production, which activates KATP, in turn attenuating neuronal excitability.
- **Neurotransmitter Function:** The KD interferes with the concentration of gamma aminobutyric acid, or GABA. There is evidence of increased GABA levels in the cerebrospinal fluid of patients that follow a ketogenic diet. GABA is a major inhibitory neurotransmitter.
- **Microbiome:** Several metabolic pathways are known to be modulated by the gut microbiota. Olson et al. (2018) demonstrated the impact of gut microbiota on the anti-seizure effect of KD. She found that KD modifies the gut microbiota, with a decrease in alpha-diversity and increases in the putatively beneficial bacteria *Akkermansia muciniphila* and *Parabacteroides sp*. This microbiota transformation leads to changes in the colonic luminal metabolome, with a decrease in gamma-glutamyl amino acids. This increases the GABA/glutamate content in the brain by decreasing gamma-glutamyl amino acids in the blood (Olson et al., 2018). In an acute electroshock model, it is reported that KD confers protection against seizures. Moreover, KD decreases the frequency of spontaneous seizures in Kcna1 knockout mice (Kim et al., 2015. Overall, changes in the gut microbiota associated with adherence to a KD seem to be important for seizure protection.
- **Inflammation:** The role of inflammatory cytokines in epilepsy is well known, and there is evidence that KD also interferes with pro-inflammatory cytokines. Dupuis et al. (2015) showed a peripheral and brain reduction of interleukin 1β and other pro-inflammatory cytokines in rats treated with KD in the LPS model.

Dementia and Alzheimer's Disease

Adapted from de Crom et al.

Diet has gained increasing interest as a target for developing preventive opportunities against dementia, as it impacts several mechanisms underlying dementia, including oxidative stress, inflammation, and vascular abnormalities. Accordingly, numerous studies have linked adherence to healthy dietary patterns to a slower rate of cognitive decline [1] and a decreased risk of dementia [2]. Although such healthy dietary patterns may be sub-optimal for brain health. Therefore, the Mediterranean-Dietary Approaches to Stop Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet has been developed [3], to uniquely emphasize foods linked to brain health, such as green leafy vegetables [4, 5] and berries [6]. Adherence to the MIND diet has indeed been linked to better cognitive performance [7, 8], less cognitive decline [3, 9,10,11], and a lower dementia risk [12, 13]. A general description of guidelines, recommendations and restrictions are outlined in Table 5.2.

Mediterranean-DASH = MIND Diet Guidelines and Restrictions	
At least three servings of whole grains a day	+
Green leafy vegetables (such as salad) at least six times a week	+
Other vegetables at least once a day	+
Berries at least twice a week	+
Red meat less than four times a week	+
Fish at least once a week	+
Poultry at least twice a week	+
Beans more than three times a week	+
Nuts at least five times a week	+
Use predominantly olive oil for cooking	+
Fried or fast food less than once a week	-
Less than a tablespoon of butter or margarine a day	-
Less than a serving of cheese a week	-
Less than five pastries or sweets a week	-
One glass of wine or other alcoholic drink a day	-

Table 5.2 Principles of the MIND Diet. The MIND diet includes 10 food groups to incorporate with frequency and 5 groups to limit. The plus (+) sign indicates inclusion and the minus (-) sign exclusion as indicated.

While both the MIND and Mediterranean diets yield similar reductions in Alzheimer's risk, the MIND diet is more flexible, which may make it easier to follow for some Americans. For example, the Mediterranean diet recommends eating fish multiple days a week, which can be a challenge.

Another interesting takeaway from the research describing MIND's effectiveness is that you don't have to have a perfect diet to benefit. While adults who followed the diet most closely (an average score of 9.6 points out of 15) saw the biggest drop in their Alzheimer's risk, the ones who scored in the middle (7.5 points) still cut their risk by over a third. Consider targeting just one or two of the habits above to improve your score — and your brain health.

Dysphagia and Diet

Adapted from the NIH's Informational Page on Dysphagia

Patients with various neurological or other disorders may suffer with dysphagia. This section includes a brief definition, description, and strategies for mitigation.

Defined. Patients with dysphagia have difficulty swallowing and may even experience pain while swallowing (odynophagia). Some people may be completely unable to swallow or may have trouble safely swallowing liquids, foods, or saliva. When that happens, eating becomes a challenge. Often, dysphagia makes it difficult to take in enough calories and fluids to nourish the body and can lead to additional serious medical problems.

Causes of dysphagia. Dysphagia occurs when there is a problem with the neural control or the structures involved in any part of the swallowing process. Weak tongue or cheek muscles may make it hard to move food around in the mouth for chewing. A stroke, Alzheimer's disease, or other disorder may make it difficult to start the swallowing response, a stimulus that allows food and liquids to move safely through the throat. Another difficulty can occur when weak throat muscles, such as after cancer surgery, cannot move all the food toward the stomach. Dysphagia may also result from disorders of the esophagus. Dysphagia has many possible causes and happens most frequently in older adults. Any condition that weakens or damages the muscles and nerves used for swallowing may cause dysphagia. For example, people with diseases of the nervous system, such as cerebral palsy or Parkinson's disease, often have problems swallowing. Additionally, stroke or head injury may weaken or affect the coordination of the swallowing muscles or limit sensation in the mouth and throat.

People born with abnormalities of the swallowing mechanism may not be able to swallow normally. Infants who are born with an opening in the roof of the mouth (cleft palate) are unable to suck properly, which complicates nursing and drinking from a regular baby bottle. Finally, for people with dementia, memory loss and cognitive decline may make it difficult to chew and swallow.

Swallowing is a complex process. Some 50 pairs of muscles and many nerves work to receive food into the mouth, prepare it, and move it from the mouth to the stomach. This happens in three stages. During the first stage, called the oral phase, the tongue collects the food or liquid, making it ready for swallowing. The tongue and jaw move solid food around in the mouth so it can be chewed. Chewing makes solid food the right size and texture to swallow by mixing the food with saliva. Saliva softens and moistens the food to make swallowing easier. Normally, the only solid we swallow without chewing is in the form of a pill or caplet. Everything else that we swallow is in the form of a liquid, a puree, or a chewed solid.

The second stage begins when the tongue pushes the food or liquid to the back of the mouth. This triggers a swallowing response that passes the food through the pharynx, or throat (see figure). During this phase, called the pharyngeal phase, the larynx (voice box) closes tightly and breathing stops to prevent food or liquid from entering the airway and lungs.

The third stage begins when food or liquid enters the esophagus, the tube that carries food and liquid to the stomach. The passage through the esophagus, called the esophageal phase, usually occurs in about three seconds, depending on the texture or consistency of the food, but can take slightly longer in some cases, such as when swallowing a pill.

Treatments for Dysphagia. There are different treatments for various types of dysphagia. Medical doctors and speech-language pathologists who evaluate and treat swallowing disorders use a variety of tests that allow them to look at the stages of the swallowing process. One test, the Flexible Endoscopic Evaluation of Swallowing with Sensory Testing (FEESST), uses a lighted fiberoptic tube, or endoscope, to view the mouth and throat while examining how the swallowing mechanism responds to such stimuli as a puff of air, food, or liquids.

A videofluoroscopic swallow study (VFSS) is a test in which a clinician takes a videotaped X-ray of the entire swallowing process by having patients consume several foods or liquids along with the mineral barium to improve visibility of the digestive tract. Such images help identify where in the swallowing process patients are experiencing problems. Speech-language pathologists use this method to explore what changes can be made to offer a safe strategy when swallowing. The changes may be in food texture, size, head and neck posture, or behavioral maneuvers, such as "chin tuck," a strategy in which patients tuck their chin so that food and other substances do not enter the trachea when swallowing. If the patient is unable to swallow safely despite rehabilitation strategies, then medical or surgical intervention may be necessary for the short-term as they recover. In progressive conditions such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), a feeding tube in the stomach may be necessary for the long-term.

For some people, treatment may involve muscle exercises to strengthen weak facial muscles or to improve coordination. For others, treatment may involve learning to eat in a special way. For example, some people may have to eat with their head turned to one side or looking straight ahead. Preparing food in a certain way or avoiding certain foods may help in some situations. For instance, people who cannot swallow thin liquids may need to add special thickeners to their drinks. Other people may have to avoid hot or cold foods or drinks.

For some, however, consuming enough foods and liquids by mouth may no longer be possible. These individuals must use other methods to nourish their bodies. Usually this involves a feeding system, such as a feeding tube, that bypasses or supplements the part of the swallowing mechanism that is not working normally.

Gut-Brain Axis

Adapted from Carabotti et al. and Verduci et al.

Insights into gut-brain crosstalk have revealed a complex communication system that not only ensures the proper maintenance of gastrointestinal homeostasis, but is likely to have multiple effects on affect, motivation, and higher cognitive functions. The complexity of these interactions is enclosed in the denomination of "gut-brain axis" (GBA) [1]. Its role is to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling. The mechanisms underlying GBA communications involve neuro-immuno-endocrine mediators.

This bidirectional communication network includes the central nervous system (CNS), both brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS), and the hypothalamic pituitary adrenal (HPA) axis. The autonomic system, with the sympathetic and parasympathetic limbs, drives both afferent signals, arising from the lumen and transmitted though enteric, spinal, and vagal pathways to CNS, and efferent signals from CNS to the intestinal wall. The HPA axis is considered the core stress efferent axis that coordinates the adaptive responses of the organism to stressors of any kind [2]. It is a part of the limbic system, a crucial zone of the brain involved in memory and emotional responses. Environmental stress, as well as elevated systemic pro-inflammatory cytokines, activate this system that, through secretion of the corticotropin-releasing factor (CRF) from the hypothalamus, stimulates adrenocorticotropic hormone (ACTH) secretion from pituitary gland that, in turn, leads to cortisol release from the adrenal glands. Cortisol is a major stress hormone that affects many human organs, including the brain.

Both neural and hormonal lines of communication combine to allow brain to influence the activities of intestinal functional effector cells, such as immune cells, epithelial cells, enteric neurons, smooth muscle cells, interstitial cells of Cajal, and enterochromaffin cells. These same cells, on the other hand, are under the influence of the gut microbiota [3], whose contributing role in brain-gut reciprocal communications has recently been uncovered and continues to be investigated. Figure 5.1 illustrates the bidirectional communication between the brain and gut via hormonal and neural pathways, where a tipping or leverage point in this diagram is diet. A diet rich in fiber serves a fuel source to resident microbes of the colon, promoting production of short chain fatty acids (SCFAs) and branched-chain fatty acids (BCFAs). Further, gut microbes themselves are known producers of some neurotransmitters which can act locally. The concept of a microbiome-mediated gut-brain axis is emerging and being investigated.

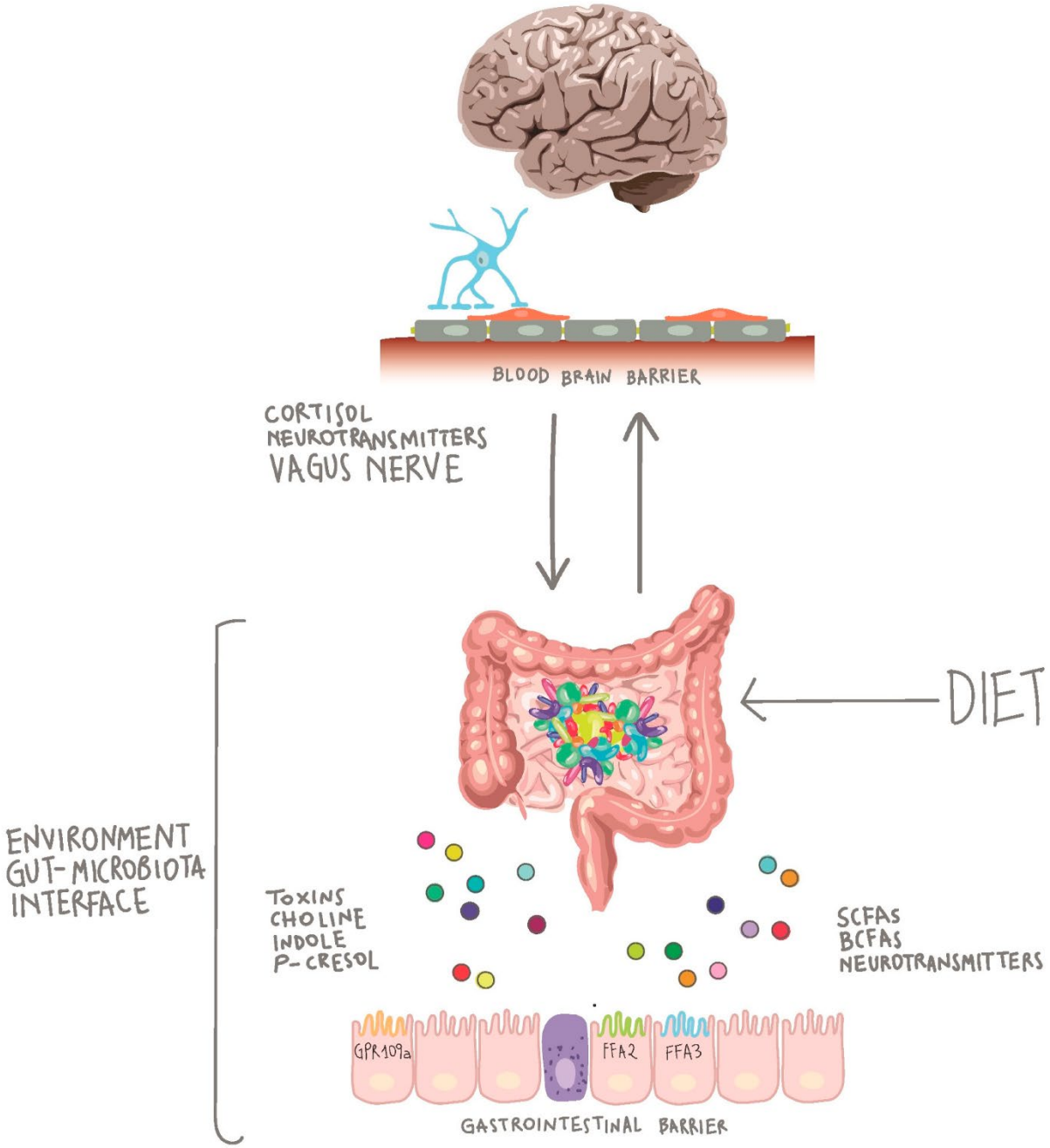

Figure 5.1 The microbiome-mediated gut-brain axis.

Precision Nutrition & Advanced Culinary Medicine E-Book

Module 6 – Cancer

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Introduction, Precision Nutrition, and Cancer Therapy

Adapted from Lelièvre SA et al.

Cancer is a global burden. The most common types of cancer in the United States are illustrated in Figure 6.1, with new breast and prostate cancer diagnoses expected to overshadow the other types in frequency. Lung cancer is the leading cancer killer in both men and women in the United States.

According to W.H.O., 30% of cancers might be linked to dietary factors in industrialized countries. Cancers of the colon, rectum, prostate, oral cavity, larynx, pharynx, esophagus, stomach, liver, pancreas, uterus, endometrium, kidney and breast are those listed by W.H.O. as influenced by nutrition.[11; 9]

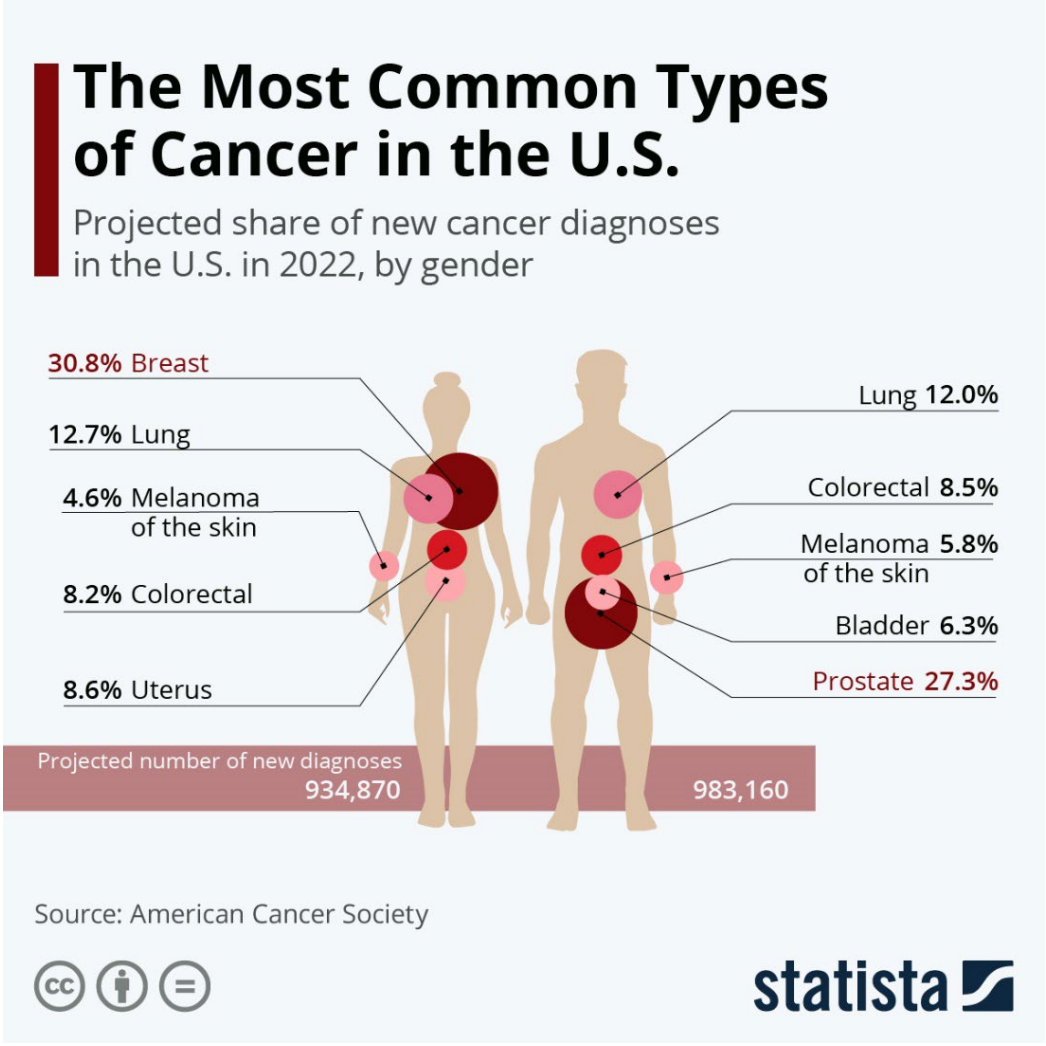

Figure 6.1 The Most Common Types of Cancer in the U.S.

Adapted from Reglero et al.

Over the years, numerous epidemiological studies have been carried out to link the diet with cancer, either from a preventive approach or by associating the consumption of certain food products with tumor generation and growth. Many of these reports are summarized in this chapter, in tables specific to the most prevalent types of cancer in the United States. Generally, a whole-foods diet approach that emulates principles of the Mediterranean diet have emerged as significant factors to reduce risk for developing common cancers.

However, in parallel to the development of precision therapies in medicine, precision nutrition is an emerging science that relies on well-established factors such as genetic and epigenetic variation [30] and the microbiome [31]. It has recently been shown that the treatment of human cell lines with different bioactive foodstuffs influences their physiological attributes depending on their ability to influence the expression of different genes [32]. The possibility of using nutritional therapies against cancer, as a complementary medicine, is internationally accepted due to its advantages of less toxicity and better acceptance by patients [33]. In the case of breast cancer, complementary phytochemical therapy in adjuvant treatments has been proposed both with preventive effects and during conventional treatments after diagnosis [34], concluding that nutritional strategies can be effective for prevention of relapse [35].

Epidemiological studies triggered further research in terms of molecular mechanisms, which have significantly improved the effectiveness of **phytotherapy**, entering the context of precision nutrition [36]. Recent studies on the association between prevention, treatment, and recurrence of cancer suggest the benefit of investigating the link between specific food components and certain health outcomes [37]. Since very specific therapeutic targets must be reached, precision nutrition must be based on individual foodstuffs with well-established mechanisms of action at the molecular level in terms of gene expression modulation and signaling pathways involved in proliferation, invasion, angiogenesis, and metastasis or apoptosis [38]. For example, it has been shown that it is possible to attack genetic instability associated with cancer through nutritional strategies that inhibit proliferative signaling, attenuate oncogenic metabolism, and block inflammation [39].

The biological activity of **food polyphenols**, a broad family of compounds with representatives in virtually all foods, has been specially studied for decades, since they have in common an intense antioxidant activity that suggests other potential health outcomes, for example in breast cancer [40]. Recently, intensive research has been carried out to determine the preventive or therapeutic activity of different natural phenolic compounds [41], opening ways for its application in new treatments of various types of cancers such as breast [42,43,44,45], colon [46], or prostate [47,48]. Some synthetic phenolic compounds have also been successfully studied for the treatment of some cancers [49]. In addition to polyphenols, curcumin (diferuloylmethane) is one of the most studied foodstuffs in recent years as a potential therapeutic product for cancer and more specifically for leukemia [50]. Traditional food products, such as rosemary extract, have been proposed as potential ingredients of precision nutritional supplements in cancer therapy,

identifying molecular mechanisms related to the effects and the interactions with currently used anticancer agents [51]. In the case of colorectal cancer, lipid-metabolism-related genes have acquired relevant interest for precision nutrition therapies, since a wide range of tumorigenic steps can be influenced by lipid metabolism, both in primary tumors and distal metastasis [52]. Certain therapeutic strategies based in diet patterns during adjuvant treatments are also sometimes considered as precision therapies [53]. Finally, multi-targeting profiles of food ingredients are being investigated regarding their potential roles triggering anti-cancer molecular mechanisms through the modulation of certain gene expressions or signaling pathways [54]. Lung, breast, prostate, and colon cancers have the highest overall incidence and represent 36.4% of the total diagnosis according to GLOBOCAN 2018, a report that gathers data from the International Agency for Research on Cancer of the World Health Organization [1]. Besides their high occurrence, these types of cancer add up to a mortality rate that reaches 49.2% of the diagnosed cases. In addition, blood malignancies occur with a rate of 6.5%, an incidence particularly worrying as it is the highest in children and young adults.

In the last five years, international scientific production related to new basic and translational discoveries on cancer has grown by 5% annually. Lung, colon, breast, prostate, and leukemia cancers account for 51% of scientific publications on cancer in this period (Web of Science, Clarivate Analytics, Philadelphia, PA, USA). Recently, an increasing number of investigations based on genomics and epigenomics are focusing on the improvement of tumor classification, the relationship between cancer and microbiota, or the discovery of new therapeutic targets in metabolism, to develop specific therapies in the context of precision medicine.

Nutritional Considerations in Cancer Prevention, Treatment, and Recovery

COLORECTAL CANCER

From Veettil SK et al.

Colorectal cancer (CRC) is the third most diagnosed cancer among men and the second most common cancer among women worldwide.1 The etiology of CRC is multifactorial, with both genetic and environmental factors playing a role.2 Evidence suggests that modifiable lifestyle factors, including excess adiposity, poor diet, and physical inactivity, play an important role in the occurrence and progression of this disease.2,3

Several systematic reviews with meta-analysis of prospective observational studies have summarized evidence for the associations between dietary factors (e.g., foods and food groups, beverages, alcohol, macronutrients, and micronutrients) and the incidence of CRC. Interestingly, animal protein (particularly red meat) has emerged as a dietary factor which can increase one's risk for developing colorectal cancer. A summary of epidemiological studies examining the association of red meat intake with CRC risk are summarized in Table 6.1. To reduce risk of developing CRC, patients should incorporate plenty of dietary fiber, foods rich in Calcium (such as dairy products and yogurt), whole grains, vegetables, and fruits.

Author, Year, Country	Study Design	Result
Willett WC, 1990, USA	Observational	Positive Association: risk ratio (RR) of CRC in women who ate beef, pork or lamb every day was 2.49, as compared with those reporting <1 serving per month
Norat A, 2005, 10 European Countries	Case-Control	Positive Association: high intake (>160 g/day) group had a risk 1.4-fold as compared with the lowest intake (<20 g/day)
Chao A, 2005, USA	Observational	Positive Association: long term consumption increased the risk of CRC in the distal large intestine
Cross AJ, 2010, USA	Observational	Positive association: Heme iron, nitrite, heterocyclic amines from meat may explain associations
Chan DS, 2011, N/A	Meta-analysis of 10 cohort studies	Positive Association: 17% increased risk per 100g per day of red meat and an 18% increase per 50g per day of processed meat

Table 6.1 Summary of epidemiological studies examining the association of red meat intake with colorectal cancer (CRC) Adapted from Thanikachalam K et al.

BREAST CANCER

Adapted from Buja et al.

Breast cancer (BC) is the most frequently diagnosed female cancer, accounting for 29% of cancers in women [1]. It is important for primary prevention to include reducing modifiable risk factors, such as obesity, a sedentary lifestyle, and a poor diet. Each of these factors can have various effects, depending on breast tissue type and age (premenopausal and menopausal).

As concerns diet, the role of alcohol as a risk factor has been well established: the results of the 2011 EPIC (European Prospective Investigation into Cancer and Nutrition) survey found that 5% of BCs could be attributable to alcohol consumption [2].

Numerous studies have addressed the role of several other foods too, sometimes reporting divergent results. For example, according to the EPIC survey, a diet rich in saturated fat is associated with a higher risk of estrogen- and progesterone-positive cancer, with a significantly higher hazard ratio [3]. Similar results emerged from a Swedish cohort survey, in which a high dietary fat consumption seemed to lead to a significant increase in the risk of developing BC [4]. On the other hand, a case-control survey conducted in China in 2008 found no significant association between the various types of dietary fat and the odds of cancer [5]. Red meat and animal proteins seem to be associated with an increase in the risk of neoplastic disease, suggesting that consuming them in large amounts anticipates menarche, and this is recognized as a risk factor and predictor of BC [6]. Several epidemiological studies have shown that consuming soy products is associated with a lower incidence of hormone-related tumors, including BC, due to the properties of isoflavones and phytoestrogens

Author, Year	**Study Design**	**Result**
Gandini, 2000	Random effects model; fixed effects model	High Veg consumption, High VitC and β-carotene intake w/ protective effect against BC
Trock, 2006	Random effects model & fixed effects model	High soy intake was modestly associated with a lower BC risk
Dong, 2011	Random effects model	Total dairy food consumption significant inversely associated with BC risk
Dong, 2011	Random effects model	Dietary soy isoflavone intake was associated w/ a significantly reduced risk of BC in Asian populations

Table 6.2 Summary of epidemiological studies examining the association of dietary trends and food compounds with breast cancer (BC); adapted from Buja et al.

PROSTATE CANCER

Matsushita M, Fujita K, Nonomura N. Influence of Diet and Nutrition on Prostate Cancer. *Int J Mol Sci*. 2020;21(4):1447. Published 2020 Feb 20. doi:10.3390/ijms21041447

Prostate cancer (PCa) is the second most common type of cancer and the fifth most common cause of cancer-related death in men worldwide [1]. In 2018, ~1.2 million new cases of PCa were diagnosed, and nearly 360,000 men died of PCa worldwide [1]. The incidence of PCa typically varies widely in residential areas and is ~6-fold higher in Western countries than in non-Western countries [2].

One reason for the variability in PCa incidence in residential areas concerns innate factors, such as racial differences. African Americans have the highest rate of PCa, followed by Caucasians, whereas Asians have the lowest. In general, there is a 3-fold difference between Asians and African Americans [3]. These results are likely related to differences in genetic variation and polymorphism among races; however, Japanese men who have emigrated to Western countries have an increased incidence of PCa relative to Japanese residents in Japan [4,5]. This suggests that both innate factors and environmental factors, such as lifestyle, can influence PCa development.

Various environmental factors, such as diet, obesity, smoking, and exercise, are reportedly associated with PCa. Tobacco smoking is a risk factor in many types of cancer, and similarly, in PCa, smoking is associated with a significantly increased risk of overall mortality, cancer-specific mortality, and recurrence [6,7]. Exercise therapy often results in physical and mental improvements. According to an analysis of 752 Canadians, an active lifestyle reduced PCa risk [odds ratio (OR) = 0.8, 95% confidence interval (CI) = 0.6–0.9] [8]; however, there was no clear association between exercise and PCa in a recent meta-analysis of 28,707 cases [relative risk (RR) = 1.00, 95% CI = 0.99–1.01] [9]. Other lifestyle factors such as sleep and nutrition are reported to have effects. Table 6.3 summarizes specific nutrients and/or dietary patterns shown to reduce PCa risk, along with the reported potential mechanisms of action. Table 6.4 summarizes specific nutrients and/or dietary patterns show to increase PCa risk, along with potential mechanisms of action.

The effects of diet and nutrients on PCa pathogenesis and progression have received increasing attention. Animal studies have reported that certain nutrients, including fat, protein, carbohydrates, vitamins (vitamin A, D and E), and polyphenols, are indeed involved in PCa pathogenesis, and progression through several mechanisms, including inflammation, antioxidant effects, and the effects of sex hormones. However, contrasting findings of clinical studies have deterred determining which nutrients have a positive or deleterious effect on PCa incidence and/or progression. Weak effects of single nutrients and interactions among different nutrients have resulted in controversial results among clinical studies conducted among residents with different dietary backgrounds. Therefore, it is important to assess the effect of dietary patterns that comprehensively summarize nutrient intake. It is generally believed that a healthy dietary

pattern (e.g., low in meat and high in vegetables) can help prevent PCa and lifestyle-related diseases; however, no evidence is available regrading this belief.

Influence of Diet and Nutrition on PCa Risk Reduction	
Nutrient or Dietary Pattern	**Reported Mechanism(s)**
Unsaturated fatty acids (fish or vegetable-derived oils)	Decrease in estradiol, testosterone, and androgen receptors
Vitamin A (Lycopene) from Tomatoes	Decrease in androgen metabolism; antioxidant effect
Vitamin D (Calcitriol) from fish, dairy products, mushrooms	Promotion of immune cell differentiation
Catechins from green tea	IGF-I signaling pathway and COX-2 mediated anti-inflammatory effects
Isoflavones from legumes	Estrogenic effects; antioxidant effects; inhibition of tyrosine kinase; suppression of NFκB
Prudent dietary pattern	N/A

Table 6.3 Summary of nutrients/ bioactive compounds and their reported mechanisms associated with reduced prostate cancer (PCa) risk; adapted from Matsushita et al.

Influence of Diet and Nutrition on Increasing PCa Risk	
Nutrient or Diet Pattern	**Reported Mechanism(s)**
Total fat from animal meats and butter	IL-6/STAT3 pathway, macrophage infiltration; increase in local androgens
Heterocyclic amines from well-cooked meats	Mast cell production and macrophage infiltration
Dairy products such as milks and cheese	N/A
Western dietary pattern	N/A

Table 6.4 Summary of nutrients/ bioactive compounds and their reported mechanisms associated with increased prostate cancer (PCa) risk; adapted from Matsushita et al.

Bioactive Food Compounds

Adapted from Reglero et al.

As indicated in the Introduction, recent advances in precision nutrition are related to bioactive food compounds. There are a myriad of bioactive food compounds and components in plant-based foods; a partial list includes polyphenols, phytosterols, carotenoids, tocopherols and tocotrienols. These extra-nutritional constituents typically occur in very small quantities in foods yet are intensively studied to evaluate their effects on health that begin at the cellular level.

Cancer heterogeneity makes its treatment particularly challenging. Innovative therapies for patients are continuously being tested, and progress has been made in the last years developing early diagnosis protocols and improving patient prognosis. However, despite these efforts, a high percentage of patients relapse after surgery or initial therapy. Cancer relapse involves a great number of different molecular mechanisms that vary form one patient to another. This points to precision medicine as a key element to personalize cancer treatment and prevent relapse and suggest the value of new effective and safe compounds that potentiate the effects of already-known chemotherapy agents. In this sense, the growing number of studies regarding the mechanisms of several bioactive compounds from foods in the treatment of different types of cancer open a new layer in precision cancer therapy. Its association with specific genetic targets or different molecular pathways inhibiting tumor growth and metastasis constitutes an important customization component. Some bioactive food compounds show high synergism with several chemotherapy drugs, acting as enhancers of these anti-tumor effects or even sensitizing and reverting chemotherapy resistance. In essence, bioactive food compounds and/or components could emerge as novel complementary agents that can be useful in precision nutrition therapies addressing relapse prevention.

Epigallocatechin-gallate (EGCG), a flavonoid present in green tea, has been shown to inhibit tumor cell growth and increase apoptosis, promoting tumor suppression. This compound sensitizes human colon cancer cells to 5-fluorouracil, increasing the effects of adjuvant treatment and improving prognosis, and finally reducing tumor relapse risk [68]. EGCG can also prevent lung cancer relapse in lung cancer mouse xenografts by blocking the cancer stem-cells-like growth through the modulation of the hsa-mir-485-5p/RXRα axis and downregulating protein acetylation in lung carcinoma cells [65,66]. EGCG has been also been predicted to affect several pathways involved in cell death and survival, potentially leading to a reduced cancer progression [67]. However, further molecular validations are needed in this sense.

Quercetin is another flavonoid with interesting features for relapse prevention; it is present in vegetables such as onions. Quercetin promotes apoptosis and inhibits cell proliferation by modulating important signaling targets as PI3K/Akt or NF-κB effectively eliminating prostate CSCs. It also limits cell migratory capacity and progression of prostate cancer cell lines by the downregulation of MK [71]. In breast cancer, quercetin can help preventing relapse by decreasing expression and activation levels of mTOR, PI3K and Akt proteins leading to a significant inhibition of MCF7 cancer cell proliferation [72].

Apigenin, present in fruits, vegetables, and food herbs such as parsley, is another flavonoid with potentially interesting effects for the development of precision nutrition products. This compound improves the effectiveness of adjuvant therapy with cisplatin enhancing both cytotoxicity and its anti-migratory effect on prostate cancer stem cells [57]. Apigenin also helps preventing metastasis and relapse in non-small cell lung cancer cell lines and in an in vivo orthotopic bioluminescent xenograft model by inhibiting cell migration and invasion [58].

Naringenin is another interesting flavonoid, obtained from citrus peel, shown to inhibit proliferation and to induce apoptosis in prostate cancer cells [69].

Procyanidin-B2-3,3”-di-O-gallate (B2G2) can be extracted from grape seeds and has been shown to target both differentiated cells and CSCs leading to tumor mass reduction [70].

Curcumin is another bioactive food product that has been the subject of former numerous studies. Its anti-cancer effects, due its ability to modulate critical anti-apoptotic effectors such as Bcl-xl and NF-κB, are of prominent interest in potential relapse prevention treatments. Moreover, curcumin synergizes with vesicular stomatitis virus (VSV)-based oncolytic treatments modulating antiviral responses and components of the intrinsic apoptotic pathway in a prostate cancer cell model [59]. Furthermore, in colorectal cancer, curcumin can modulate gene expression of HSPA5, SEC61B, G6PD, HMOX1, and PDE3B, affecting essential pathways like DNA replication or the cell cycle. On the other hand, the synergy of curcumin and oligomeric proanthocyanins emerges as an opportunity to develop effective therapies, since both compounds share similar molecular mechanisms [60]. Recently, relevant effects of curcumin in breast cancer cell models have been discovered, being that this compound is able to increase the expression of E-cadherin and decrease the expression of mesenchymal markers [61]. It has been also shown that curcumin enhances the effect of some targeted drugs used in cancer such as gefitinib, an EGFR inhibitor, inducing autophagy-mediated apoptosis. This observation opens opportunities for the use of this compound with treatments to prevent cancer relapse [62].

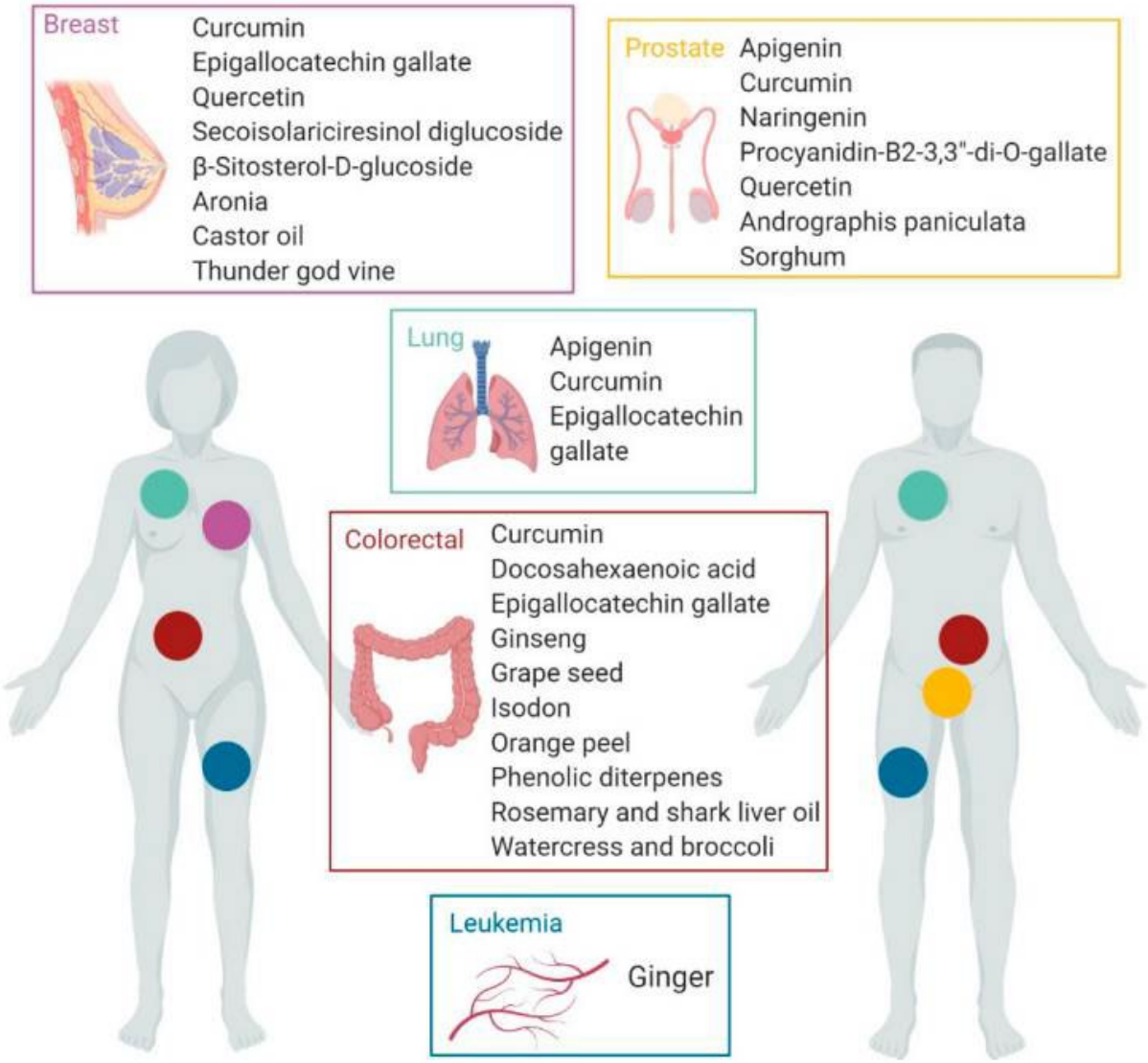

Figure 6.2 Bioactive food compounds and natural extracts with proven effects in cancer treatment. Reglero et al.

CULINARY STRATEGIES & MODIFICATIONS

American Cancer Society

Certain types of cancer and its treatment(s) can change your senses of **taste and smell**. This effect can last weeks to months. Common causes may include types of tumors in the head and neck area, radiation to the head and/or neck area, certain kinds of chemotherapy and targeted therapy, mouth sores and/or dryness due to certain treatments, and some medications used to help with other side effects or other non-cancer problems can also affect taste and smell.

Changes in taste and smell can very often affect appetite. Patients may have a reduced or altered sense of smell, or even have an enhanced sense of smell. Patients may have a bitter or metallic taste in the mouth, food may taste too salty, too sweet, or have no taste at all.

There are several strategies that patients and caregivers can employ to attempt to alleviate any or all side effects; these are summarized in Table 6.5

Strategies to Address Metallic Taste
Try using plastic forks, spoons, and knives and glass cups and plates.
Season foods with tart flavors. Use lemon wedges, lemonade, citrus fruits, vinegar, and pickled foods. (If you have a sore mouth or throat, do not do this.)
Try sugar-free lemon drops, gum, or mints.
Keep your mouth clean and brush your teeth to help ease bad tastes.
Try fresh or frozen fruits and vegetables instead of canned.
Strategies to Address Altered Taste
Counter a salty taste with added sweeteners, a sweet taste with added lemon juice and salt, and a bitter taste with added sweeteners.
Rinse your mouth with a baking soda, salt, and water mouthwash before eating to help foods taste better. (Mix 1 teaspoon salt and 1 teaspoon baking soda in 4 cups of water. Shake well before swishing and spitting.)
Serve foods cold or at room temperature. This can decrease the foods' tastes and smells, making them easier to tolerate.
If red meats taste strange, try other protein-rich foods like chicken, fish, beans or peas, tofu, nuts, seeds, eggs, or cheese.
To reduce smells, cover beverages and drink through a straw; choose foods that don't need to be cooked; and avoid eating in rooms that are stuffy or too warm.
Strategies to Promote Adequate Nutrition
Freeze fruits like cantaloupe, grapes, oranges, and watermelon, and eat them as frozen treats.
Blend fresh fruits into shakes, ice cream, or yogurt.
Try flavoring foods with new tastes or spices (onion, garlic, chili powder, basil, oregano, rosemary, tarragon, BBQ sauce, mustard, ketchup, or mint).
Try marinating meats to make them tender.

Table 6.5 Strategies to address an underlying metallic taste, altered taste, and to promote adequate food intake.

Precision Nutrition & Advanced Culinary Medicine E-Book

Module 7 – Gastrointestinal Health & Microbiome

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The Microbiome

The human gut microbiome—the collection of microorganisms residing in the gastrointestinal tract—is thought to play a role in the etiology of various diseases, including inflammatory bowel disease[1,2,3], type 2 diabetes[4,5,6], hypertension[7,8,9], and colorectal cancer[10,11,12,13]. Individual clinical blood markers, such as those for diabetes[14] and cholesterol[15], have been found to be associated with abundances of certain gut bacteria. Lifestyle habits, such as exercise, smoking and diet can impact the composition of the gut microbial community. For example, diet can profoundly influence the composition of the microbiome[16,17,18]. Similarly, physical activity has been shown to drive shifts in the composition of the gut microbiome in animal models[19,20], and there is preliminary evidence from small-cohort studies that exercise impacts the microbiome in humans as well[21,22,23,24,25]. The human gut microbiome is highly individualized, and it develops across the course of the lifespan. Research demonstrates that birth mode, vaginal versus cesarean birth, is associated with distinctions in the microbiome at a very young age. Moving forward from birth, breastfeeding versus bottle feeding practices is also associated with distinctions in the microbiome composition. Courses of antibiotic use over the lifespan, use of antibacterial items, living environment, and dietary patterns all affect the human microbiome. Therefore, a person's microbiome is highly unique, shaped by one's own personal dietary preferences, genetics, and environmental exposures. This is one of the unique and challenging aspects of leveraging microbiome science at the population level.

Despite the growth in microbiome research in recent years, large-scale human studies that integrate gut microbiome profiles with host clinical blood phenotypes, dietary, lifestyle data, disease diagnoses and medication usage remain scarce. These dense phenotyping studies on large cohorts are crucial for validating associations established in varying contexts, using sparser data from smaller cohorts.

Inflammatory Bowel Disease (IBD)

Introduction

Inflammatory bowel disease (IBD) is characterized by repetitive episodes of inflammation of the gastrointestinal tract caused by an abnormal immune response to gut microflora. Inflammatory bowel disease encompasses two types of idiopathic intestinal disease that are differentiated by their location and depth of involvement in the bowel wall. **Ulcerative colitis (UC)** involves diffuse inflammation of the colonic mucosa. Most often UC affects the rectum (proctitis), but it may extend into the sigmoid (proctosigmoiditis), beyond the sigmoid (distal ulcerative colitis), or include the entire colon up to the cecum (pancolitis). **Crohn disease (CD)** results in transmural ulceration of any portion of the gastrointestinal tract (GI) most often affecting the terminal ileum and colon. Both diseases are classified by extent (mild, moderate, or severe) and location. CD also is classified by phenotype— inflammatory, stricturing, or penetrating. [1][2][3]

Besides the GI tract, both Crohn's disease and ulcerative colitis have many extraintestinal manifestations. While in most patients the disorders can be distinguished, in at least 10% of patients, the features are so similar that it is not possible to initially differentiate between the two disorders.

Both disorders have a genetic predisposition; neither is curable, and they both carry enormous morbidity. Finally, both increase the risk of colorectal cancer.

Etiology

Inflammatory bowel disease (IBD) occurs in genetically susceptible individuals after an inappropriate immune response to the intestinal flora.

To date, the cause of IBD remains a mystery. Many causes have been implicated but none is universally present in all patients. The one consistent feature of Crohn disease is that it has a strong link with tobacco. On the other hand, it appears that smoking protects against ulcerative colitis. The role of diet remains debatable. A few diets have been examined for their efficacy to control symptoms and/or mitigate inflammation, such as the specific carbohydrate diet (SCD) and exclusive enteral nutrition (EEN).

The CARD15 gene has been associated with IBD but because of its polymorphic features, it is not possible to determine which part of the GI tract will be affected. The role of genes in ulcerative colitis is not as strong as in Crohn disease.

Epidemiology

The North American incidence of inflammatory bowel disease (IBD) ranges from 2.2 to 19.2 cases per 100,000 person-years for ulcerative colitis and 3.1 to 20.2 cases per 200,000 person-years for CD. Prevalence in the United States of adult ulcerative colitis was 238 per 100,000 population and 201 per 100,000 population from data in a large study based on insurance claims. IBD is much more prevalent in North America and Europe than in Asia or Africa. Although most IBD occurs in people age 15 to 30 years, up to 25% of patients will develop IBD by adolescence. There appears to be a bimodal distribution with a second peak of 10 to 15 percent of cases developing after the age of 60. Crohn's disease is slightly more common in females compared to males, but ulcerative colitis appears to be equally present in both genders. IBD is generally a disorder of developed countries and colder climates.

Pathophysiology

The **intestinal immune system** is key to the pathogenesis of inflammatory bowel disease (IBD). The intestinal epithelium prevents bacteria or antigen entry into the circulation by sealed intercellular junctions. In IBD, these **junctions are defective from either a primary barrier function failure or because of severe inflammation**. Additional protective mechanisms include mucus production by goblet cells and Paneth cells secretion of a-defensins with intrinsic antimicrobial activity. Excessive inflammatory reactions lead to continued deterioration of the epithelium and further exposure to intestinal microbes thereby furthering worsening the inflammation.

In ulcerative colitis, there is always mucosal inflammation that leads to edema, ulcers, bleeding, and electrolyte losses. The inflammation in ulcerative colitis usually starts in the rectum and progresses in an uninterrupted fashion to the proximal colon. In Crohn disease, there are skip lesions. Skip lesions refers to a phenomenon where physiologically "normal" segments of the bowel are interrupted by diseased portions. In contrast, in nearly 20% of patients with UC, the disease remains confined to the rectum. Pancolitis is seen in about 15% of patients. As the disorder becomes chronic, the colon becomes more rigid and short with a loss of the haustral markings leading to a "lead-pipe appearance" on a barium enema.

Crohn disease can affect any segment of the GI tract; the disease may induce strictures, inflammation or lead to the development of fistulas. The key feature of Crohn disease is that it involves all layers of the bowel (transmural; from lumen to serosa). During the later phase of the disease, the mucosa will reveal a cobblestone appearance due to the linear ulcers between the normal mucosa. Crohn disease most generally affects the colon and ileum and only 5% of cases affect the gastroduodenal segments. Sparing of the rectum is typical of Crohn disease but anorectal complications like fistulas and abscesses are very common.

UC predisposes patients to the extraintestinal involvement of the skin, eyes, and bones. Most commonly these include inflammatory arthropathies and primary sclerosing cholangitis. CD preferentially attacks the ileum and colon but can involve the esophagus, duodenum, or stomach. Pediatric-onset cases have greater upper GI tract involvement. As in the case of UC, CD predisposes patients to extraintestinal manifestations including arthritis, aphthous stomatitis, uveitis, erythema nodosum, and ankylosing spondyloarthropathy. [5][6]

In Crohn's disease, the incidence of kidney disease and gallstones is high because of malabsorption of bile salts and fatty acids. Patients with Crohn disease who undergo resection of the ileum but have an intact colon are also more likely to develop calcium oxalate renal stones.

Evaluation

Diagnosing inflammatory bowel disease (IBD) requires a combination of clinical findings, inflammatory laboratory markers, imaging findings, and endoscopic biopsies. Hematologic findings include microcytic anemia, leukocytosis, and thrombocytosis, inflammatory markers such as the erythrocyte sedimentation rate (ESR), and high-sensitivity C-reactive protein (hsCRP) are commonly elevated.[7][8]

In some patients, the diagnosis may require ruling out parasitic diseases like giardia, amebiasis, strongyloidiasis, and tuberculosis.

A complete blood count will identify anemia, leukocytosis, and albumin levels. Fecal calprotectin levels can be used as a marker for intestinal inflammation. Levels of perinuclear antineutrophilic cytoplasmic and anti-saccharomyces cerevisiae antibodies may be elevated in Crohn's disease. Finally, stool studies must be done to rule out ova and parasitic organisms.

The abdominal x-ray can assess for the presence of free air, bowel obstruction, or toxic megacolon. Barium studies are done to characterize the bowel disease; a lead pipe appearance indicates ulcerative colitis; sparing of the rectum is indicative of Crohn disease and thumb printing is indicative of mucosal inflammation. Further, the barium studies may reveal skip lesions and stricture formation in the ileum, which are indicative of Crohn disease.

Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) have all been used in the diagnosis of IBD or to assess for complications. US usage in trained individuals can evaluate the right lower quadrant for ileal disease. MRI can evaluate for rectal fistulas. Most commonly, CT is employed to evaluate for perforation or bowel obstruction. CT enterography can be helpful in assessing for strictures or in operative planning.

Endoscopy evaluation with either esophagogastroduodenoscopy, colonoscopy, or both is essential to obtaining biopsies to confirm a diagnosis of IBD.

Treatment/Management

The goal of treatment is to induce **remission** for either UC or CD. Remission is complete absence of symptoms and underlying inflammation; patients diagnosed with IBD can experience remission for years to decades. Treatment of IBD is divided into the management of mild, moderate, and severe disease. Agents formerly reserved for the more severe disease are now employed sooner. UC treatment depends greatly on the extent of the disease and the presence of extraintestinal manifestations. For those with mild to moderate disease limited to the rectum, amino salicylate agents like mesalamine are the mainstays. Mesalamine is administered rectally but may be combined with oral therapy to induce or maintain remission. For those patients with the moderate disease who are refractory to mescaline, oral glucocorticoids or immunomodulators such as TNF-alpha monoclonal antibodies (infliximab) may be an option. Up to 25% of all UC patients will require total colectomy for the uncontrolled disease. Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for elective cases.[9][10][11]

Flareups are usually managed with corticosteroid therapy. For those who have more than 1-2 flareups a year, the use of anti-TNF agents or other immunosuppressive is recommended.

CD treatment depends on the portion of the GI tract involved, the degree of fistulizing or stricturing, and any extraintestinal complications. Treatment of mild ileocecal disease is usually begun with mesalamine, which can be further augmented with the use of oral budesonide, a steroid with significant first pass metabolization to limit systemic side effects. For more extensive disease, systemic steroid therapy with prednisone is necessary. The goal is to wean these steroids within six weeks. In those patients who cannot wean, an immunomodulating agent like 6-mercaptopurine, azathioprine, or low-dose methotrexate is added. In those patients with moderate to severe disease, anti-tumor necrosis factor (anti-TNF) should be initiated. Before initiating biologic therapy, patients must complete a purified protein derivative (PPD) test to assess for latent tuberculosis. Surgical treatment may be necessary for those with severe fistulizing disease including diverting ostomy.[1][12][13]

It is vital to assess the bone density in patients who are administered steroids; osteoporosis has significant morbidity in these patients. If steroid use for more than three months is expected, then calcium supplements and bisphosphonates should be introduced.

IBD & Microbiome

Adapted from Zhu et al.

Currently, many studies have found that the composition of the gut microbiome in IBD are significantly altered, which is considered to contribute to this immune disorder (Glassner et al., 2020). A probable mechanism is that the metabolites of the microbiota regulate metabolic pathways and inflammatory signal transduction thereby affecting the host immune system. On the other hand, the gut microbiota may affect the gut immunity through adherent bacteria. Chen et al. reports that in pediatric IBD, adherent bacteria attached to the terminal ileum were associated with elevated Th17 cells and SIgA responses (Chen et al.). Previous studies of adherent bacteria mainly rely on models of immortal cell lines, which cannot reproduce the tissue-like environment. To address limitations, Mayorgas et al. established a human colonic organoids model which represents a promising tool to study the cross talk between Adherent-invasive Escherichia coli and intestinal epithelial cells (Mayorgas et al., 2021).

Studies on the microbial change in pharmaceutical treatment of IBD provide additional evidence for the microbial contribution in IBD pathogenesis. Dai et al. investigated the pharmaceutical mechanism of mesalamine in the treatment of UC through 16S sequencing and metabolomics (Dai et al.). Mesalamine is a radical scavenger and antioxidant, often used to treat UC. The authors observed that the abundance of some bacteria and metabolites were reversed toward the healthy status after mesalamine treatment. Similarly, as summarized in this issue by Li et al., many natural products may exert their therapeutic effects on the gut microbiota in the treatment of IBD (Li et al.). These studies reveal possible molecular mechanisms of naturally derived polysaccharides from plants, seaweeds, and mushrooms in the treatment of IBD, and identified many potential clinical therapeutic targets. In the same direction, Guo et al. reports that ginger can significantly increase the diversity of intestinal microbiome and alleviate the severity of UC (Guo et al.). This study suggests that the abnormality of the microbiome is closely related to amino acid metabolism, oxidative phosphorylation, protein translation, and ribosome biogenesis. The study of Zhao et al. is unique in utilizing a nano-targeted drug delivery system to achieve a highly efficient delivery of berberine (Zhao et al.), which effectively regulated inflammation and reconstructed the intestinal microbial community.

Collectively, studies have demonstrated that the microbiome is a key lever in the diagnosis and progression of IBD. Further, microbiome science has expanded to identify key dietary patterns and even foods that have beneficial versus deleterious effects on the diversity and functional capacity of the gut microbiome (Figure 7.1). Beneficial nutrients and foods increase alpha-diversity and beneficial bacteria populations while decreasing pathobionts. They also increase protective mucus secretions, improve tight junctions and the production of antimicrobial molecules. The effects on immune cells are also illustrated in Figure 7.1, with increasing Treg cell numbers and production of anti-inflammatory cytokines. In contrast, harmful nutrients/ foods decrease alpha-diversity, beneficial bacterial levels and increase pathobionts, thereby decreasing mucus secretions and reducing the strength of tight junctions. Concurrent changes in immune

cells include increasing Th1/Th2, Th17 as well as pro-inflammatory cytokines that go on to further exacerbate damage to mucosal immunity, creating a vicious cycle of dysbiosis, inflammation, and epithelial damage.

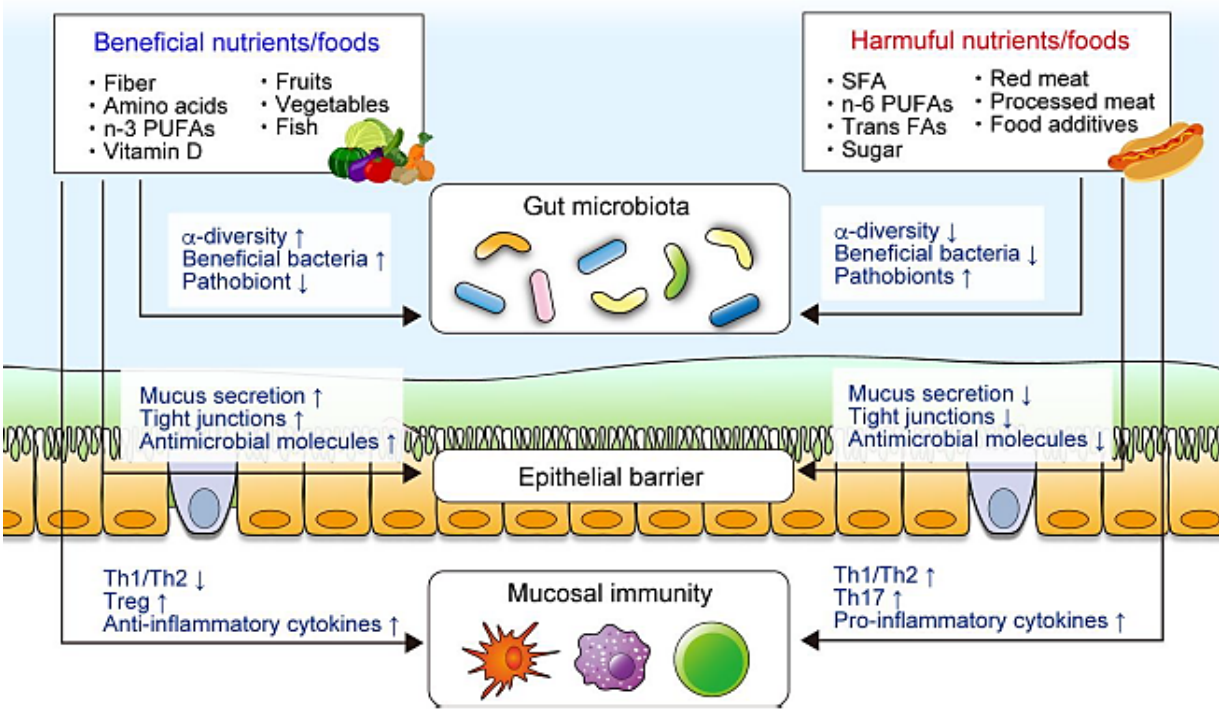

Figure 7.1 Nutrients and foods in the pathogenesis of inflammatory bowel disease. Epidemiological, clinical, and animal studies have demonstrated that certain components of diet are associated with IBD. Diet plays a critical role in intestinal homeostasis, including the gut microbiota, intestinal mucosal barrier, and mucosal immune system. Dietary patterns directly modulate the mucosal barrier and immunity, whereas diet-microbiota interaction also regulates the intestinal homeostasis.

Precision Nutrition in IBD – an Opportunity for new Research

Adapted from Hurtado-Lorenzo et al.

The Crohn's & Colitis Foundation has established a Precision Nutrition (PN) initiative to further understand how diet affects IBD, particularly at the individual patient level. This is a critical gap in the understanding and management of IBD, and an area of opportunity to make a significant impact on the quality of life of patients. The long-term goal of the PN initiative is to be able to answer the IBD patient's key question, "what should I eat," based on the patient's personal response to different foods, so that diets can be tailored to the individual clinical, biological, and lifestyle characteristics of the patient.

Driven by a multi-institutional approach, this initiative integrates several key elements needed to assemble the "IBD precision nutrition puzzle," with the overarching goal of providing unified scientific evidence to support the implementation of personalized diet recommendations for the management of IBD. Key elements are: (1) evaluation of rationally designed anti-inflammatory diets to improve disease outcomes in randomized clinical trials (orange in Figure 7.2), (2) identification of biomarkers to predict subgroups of IBD patients who are responders and nonresponders to these anti-inflammatory diets (blue in Fig. 7.2), (3) identification of proinflammatory "trigger foods" that can exacerbate symptoms or induce disease relapse (green in Fig. 7.2), and (4) development of in silico predictive tools required to design evidence-based therapeutic diets, whose efficacy can be evaluated in trials (pink in Fig 7.2). A critical unifying element at the core of this initiative is the use of artificial intelligence (AI)-based analysis of multiomics data for the identification of the biomarkers required to make predictions of patients' response to food, in order to enable precise and effective therapeutic diet recommendations.

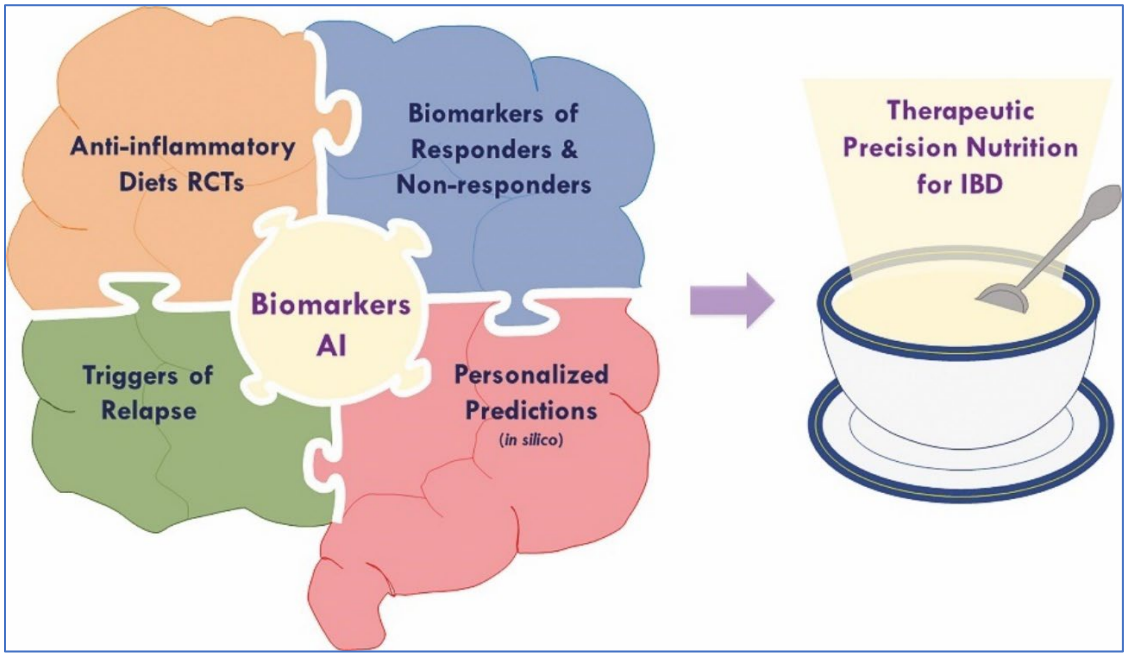

Figure 7.2 Key components of the Crohn's & Colitis Foundation's precision nutrition initiative for IBD.

Celiac Disease

Adapted from Valitutti et al.

The recognition of the causal link between gluten and celiac disease (CD) was unveiled in the 1950s [1], but the factor (or factors) that trigger the loss of immune tolerance to gluten in genetically predisposed subjects remains unknown. Since its original description, CD has most often been perceived as a pediatric condition with a peak incidence in children younger than two years of age, with more recent data suggesting that most of the cases would manifest by five years of age [2].

The worldwide prevalence of CD ranges between 1% and 2% in the general population [3,4], with most patients remaining undiagnosed due to the subtle or multiform clinical manifestations of the disease [5]. Based on more recent data, it is now appreciated that CD can present at any age with a broad range of intestinal and extra-intestinal symptoms [6,7]. Its prevalence, as in many other autoimmune diseases often found in comorbidity with CD [8], has increased over time in geographical regions characterized by a Western lifestyle [9]. This phenomenon was initially hypothesized to be secondary to the timing of gluten introduction at weaning [10], although two large, randomized, and prospective high-risk, birth cohort-controlled trials have disputed this premise by demonstrating that neither delayed nor early gluten introduction modified the risk of CD [2,11].

These findings raised doubts about another CD paradigm that suggested that genetic background and dietary gluten intake were necessary and sufficient to develop the disease. Besides the evidence that CD onset can occur years after gluten introduction into the diet [6], other evidence at odds with the old paradigm is the lack of 100% CD concordance among monozygotic twins [12]. Therefore, while genetic predisposition (including the required presence of HLA DQ2 and/or DQ8 haplotypes) and gluten exposure are necessary, they seem to be insufficient for the development of CD autoimmunity. Intestinal permeability is an additional element involved in CD pathogenesis, as a “leaky gut” might initiate the early phases of innate immune activation following the exaggerated trafficking of undigested gluten fragments from the intestinal lumen to the lamina propria [13].

Important to note, CD itself is an autoimmune condition that is distinct from gluten allergy or gluten sensitivity (Figure 7.3).

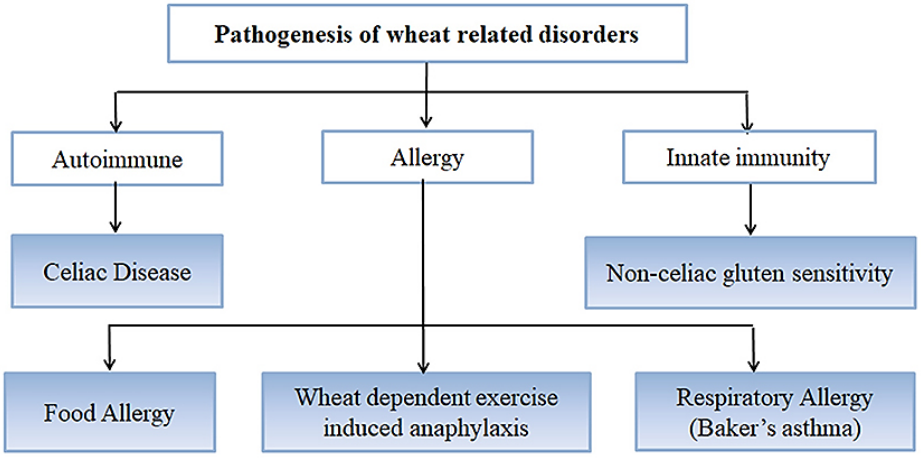

Figure 7.3. Pathogenesis of wheat-related disorders: auto-immune, allergy and innate immunity.

Celiac Disease and Microbiome

Growing evidence supports the hypothesis that changes in gut microbiome composition and function are associated with several chronic inflammatory diseases, including obesity [14], diabetes [15], inflammatory bowel disease [16] and cancer [17]. This might also be the case for CD.

In the last decades, one of the major advances in the field of microbiome studies has been the ability to apply culture-independent approaches to determine the microbiome's composition [18]. These technologies allow for the identification and quantification of components of the human microbiota by studying nucleic acids (DNA and RNA) from fecal samples or other biological samples [19], which eliminates the need for tissue cultures and allows the characterization of non-cultivable microbes.

Gut bacteria facilitate the digestion of insoluble fiber, produce vitamins such as vitamin K, and elaborate trophic and immunomodulating compounds such as short-chain fatty acids (SCFA) [24].

Moreover, they also display key immune-modulating functions within the gut. By competing for nutritional sources and producing anti-microbial molecules, beneficial gut bacteria counterbalance the growth of pathogenic bacteria and favor epithelial integrity [25,26]. Microbiome-derived SCFA can also modulate host histone deacetylase, therefore epigenetically influencing the function of innate and adaptive immune cells [27]. The impact of the gut microbiome on mucosal immunity is further demonstrated by the evidence of defects in lymphoid tissues (fewer mucosal Peyer's patches and smaller mesenteric lymph nodes) and compromised antibody production in germ-free animals [28].

Bifidobacterium and Lactobacilli Strains are players in Pathogenetic Interactions

In the pursuit of the best microbial candidate for disease immunomodulation, a few Bifidobacteria strains have been studied with considerable results. For example, in an in vitro model using peripheral blood mononuclear cell (PBMCs), both Bifidobacterium longum ES1 and Bifidobacterium bifidum ES2 have been shown to downregulate the Th1 pathway typical of CD [81].

In addition, Lindfors et al. assessed whether Bifidobacterium lactis can neutralize the toxicity of gliadin. In Caco-2 cells, they found that this strain was at least able to reduce the epithelial permeability triggered by gluten [82]. Laparra et al. evaluated Bifidobacterium longum CECT 7347 in a murine model of CD, and they found that this specific strain not only diminishes pro-inflammatory cytokine synthesis, such as tumor necrosis factor-alfa (TNF-alfa), but it also reduces jejunal architecture damage [83]. Another group has demonstrated that Bifidobacterium longum strain NCC2705 produces a serine protease inhibitor with immune-modulating features, i.e., attenuating gliadin-induced histological damage in NOD/DQ8 mice [84].

An alternative Bifidobacterium, B. infantis, seems to decrease Paneth cells and expression of alfa-defensin-5 on electronic microscopy of duodenal biopsy when administered in active CD [85]. Paneth cells are key masters of gut homeostasis in innate immunity against noxious pathogens through the release of defensins, lysozyme and phospholipase [86]. Furthermore, some evidence concerning the protective effect of Lactobacillus casei DN-114001 and E. Coli strain Nissen 1917 on gut barrier function has been reported [87].

D'Arienzo et al. analyzed the effect of Lactobacillus casei, Lactobacillus paracasei, and Lactobacillus fermentum in a transgenic mouse model expressing human DQ8. They found that L casei reduces TNF-alfa secretion and related villous blunting, while both L paracasei and L fermentum determine increased antigen-specific TNF-alfa. This suggests that, depending on the strain and on the experimental model, probiotics may have either proinflammatory or immunomodulatory properties [88,89].

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders encountered in clinical practice. It is a heterogeneous disorder with a multifactorial pathogenesis. Recent studies have demonstrated that an imbalance in gut bacterial communities, or "dysbiosis," may be a contributor to the pathophysiology of IBS. There is evidence to suggest that gut dysbiosis may lead to activation of the gut immune system with downstream effects on a variety of other factors of potential relevance to the pathophysiology of IBS.

Dietary factors are central for patients with IBS, and most patients report worsening of symptoms after intake of certain trigger food items, particularly foods containing refined carbohydrates or fat. This may be due to diet–microbiota interactions since gut microbes have an important role in the digestion of dietary components and fermentation of indigestible fibers that may directly or indirectly contribute to IBS symptoms. Food items rich in indigestible carbohydrates (i.e., fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [FODMAPs]) seem to be particularly relevant, because they can provoke IBS symptoms in susceptible individuals through osmosis and fermentation. Several studies have demonstrated the clinical efficacy of a low FODMAP diet in IBS, an effect that goes beyond the placebo response frequently reported in patients with IBS, but not clearly superior to traditional IBS dietary advice.

The clinical effect of a low FODMAP diet is partly mediated through diet–microbiota interactions; a reduction of carbohydrates, that is, the substrate for bacterial fermentation in the colon, leads to lowered gas production and thereby reduced intestinal distension. However, the physiologic responses to FODMAP intake, that is, the effect on luminal water content, gas production, and degree of luminal distension, do not seem to differ between patients with IBS and healthy controls, but colonic hypersensitivity to distension, rather than excessive gas production, seems to be the main cause of carbohydrate-related symptoms in patients with IBS. Regarding gut microbiota, a low FODMAP diet leads to substantial changes in gut microbiota composition with a decrease in gut microbes putatively associated with health, such as bifidobacteria, which may seem counterintuitive. However, the relevance of changes in the gut luminal microenvironment and changes in symptoms remain unclear. Furthermore, gut microbiota composition before starting a low FODMAP diet seems to be a predictor for the symptom response, highlighting the relevance of diet–microbiota interactions for efficacy.

Bellini et al. advocate for future uses and utility of the low FODMAP diet for patients diagnosed with IBS, proposing a dietary management flowchart that emphasizes personal optimization by way of initial clinical and dietary assessments (Figure 7.4).

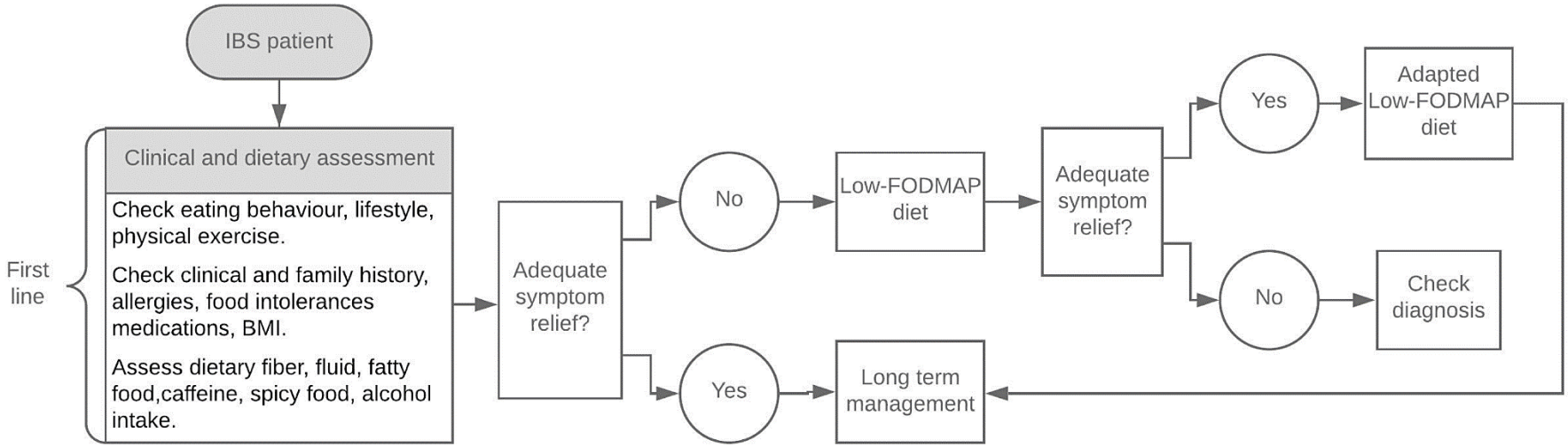

Figure 7.4 Dietary management flowchart for patients diagnosed with irritable bowel syndrome (IBS); focused on low-FODMAP approach.

Precision Nutrition & Advanced Culinary Medicine E-Book

MODULE 8 – Renal Conditions

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Chronic Kidney Disease

Adapted from NIDDK Website

Chronic kidney disease (CKD) means a patient's kidneys are damaged and can't filter blood the way they should. The disease is called "chronic" because the damage to one's kidneys happens slowly over a long period of time. This damage can cause wastes to build up in the body. CKD can also cause other health problems. The kidneys' main job is to filter extra water and wastes out of blood to make urine. To keep a body working properly, the kidneys balance the salts and minerals—such as calcium, phosphorus, sodium, and potassium—that circulate in the blood. The kidneys also make hormones that help control blood pressure, make red blood cells, and keep bones strong.

Kidney disease often can get worse over time and may lead to kidney failure. If kidneys fail, patients will need dialysis or a kidney transplant to maintain their health.

People are at risk for kidney disease if they have:

- **Diabetes.** Diabetes is the leading cause of CKD. High blood glucose, also called blood sugar, from diabetes can damage the blood vessels in the kidneys. Almost 1 in 3 people with diabetes has CKD. Type 2 diabetes is the number one cause of kidney failure. This statistic underscores the importance of managing diabetes and keeping blood sugar under control. Tight control has immense benefits by reducing the risk for kidney disease.
- **High blood pressure**. High blood pressure is the second leading cause of CKD. Like high blood glucose, high blood pressure also can damage the blood vessels in your kidneys. Almost 1 in 5 adults with high blood pressure has CKD.
- **Heart disease**. Research shows a link between kidney disease and heart disease. People with heart disease are at higher risk for kidney disease, and people with kidney disease are at higher risk for heart disease. Researchers are working to better understand the relationship between kidney disease and heart disease.
- **Family history of kidney failure**. If one's mother, father, sister, or brother has kidney failure, there is a risk for CKD. Kidney disease tends to run in families. People who have kidney disease should encourage family members to get tested. People with CDK can use tips from the family health reunion guide and speak with their family during special gatherings.

Other health problems that can cause CKD include glomerular diseases that attack blood vessels in the nephrons (the functional unit of the kidney); focal segmental glomerulosclerosis (FSGS) is such an example. Polycystic or other cyst diseases can cause fluid filled bubbles to replace normal kidney tissue. Tumors or cancer in the kidneys, as well as lupus (an auto-immune condition that may attack the skin, joints, kidneys, and brain). The chances of having kidney disease increase with age. The longer a person has had diabetes, high blood pressure, or heart disease, the more likely that they will have kidney disease.

African Americans, Hispanics, and American Indians tend to have a greater risk for CKD. The greater risk is due mostly to higher rates of diabetes and high blood pressure among these groups. Scientists are studying other possible reasons for this increased risk.

There are five stages of CKD; the criteria for determining which stage a patient falls in is decided by two GFR test at least 90 days apart. Stages 1 and 2 occur only in people whose kidneys are abnormal. For example, they may have been born with one kidney, born with kidney cysts, or have urine that backs up into the kidneys. Most people find out they have CKD at stages 3, 4, or 5. In the early stages, the risk of heart disease is higher than later stages, so efforts should be made to protect both the kidneys and the heart.

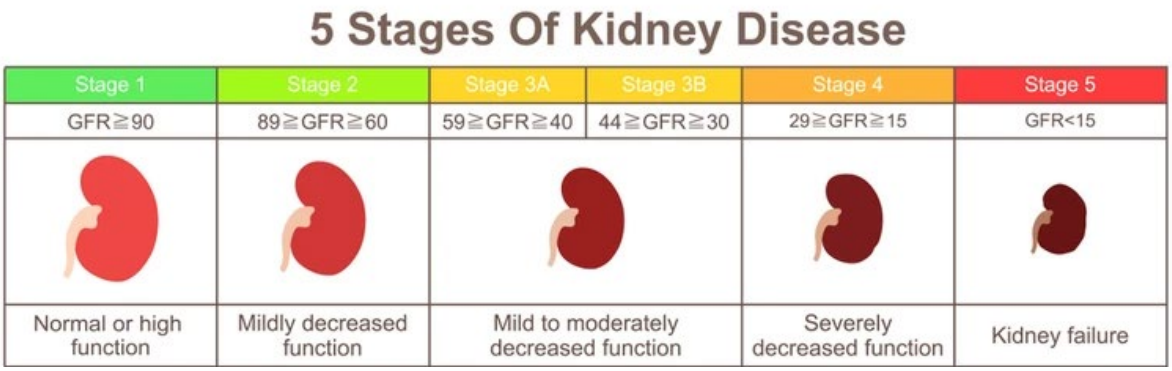

Figure 8.1 The 5 stages of CKD, based on two GFR tests separated by at least 90 days.

Nutritional Considerations

Adapted from Molina et al.

A caloric intake of 25–35 kcal/kg/day is recommended to counteract the excess resting energy expenditure secondary to inflammation and comorbidities, as well as for preserving a neutral or positive nitrogen balance. However, this recommendation should be individualized according to the patient's profile, including age, lean body mass (which is the primary determinant of energy expenditure), physical activity, and the underlying etiology of kidney disease (20, 21). According to the 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, the recommended protein intake for stable patients with ND-CKD 3–5 dialysis is 0.55–0.60 g/kg/day, which can be reduced to 0.28–0.43 g/kg/day if it is supplemented with 7–15 g/day of KAs (keto analogs) and essential AAs (amino acids). In the case of diabetic patients, guidelines suggest a higher protein intake up to 0.6–0.8 g/kg/day to glycemic control. Any intercurrent catabolic episode may require increasing energy and protein intake independently of CKD stage (22).

A modest sodium restriction (<2.3 g/day) is recommended for the management of CKD patients to achieve better volume control, reducing blood pressure (BP), and proteinuria synergistically with available pharmacologic interventions (18). A daily fiber intake of 25–30 g/day or more for CKD patients may be suggested, with this amount like recommendations for the general population (7). Potassium restriction in CKD may prevent from complying with this recommendation but in general terms CKD patients do not require aggressive dietary potassium restriction until advanced stages or if hyperkalemia risk is judged high (24–26). Recently, it has been suggested to avoid high potassium foods with poor nutritional value (i.e., bran products, or salt substitutes) and correct other causes of hyperkalemia, such as metabolic acidosis or use of renin-angiotensin-aldosterone system (RAAS) inhibitors, before restricting healthy foods (27). Given the role of calcium balance and the serum phosphate in the development of cardiovascular calcifications, several experts recommend limiting total dietary calcium intake to 800–1,000 mg/day or less (including dietary calcium, calcium supplementation, and calcium-based phosphate binders) in adults with CKD 3–4 not taking active vitamin D analogs. Although phosphate intake to 800–1,000 mg/day (800–1,300 in KTR) was recommended previously (29, 30), new guidelines suggest adjusting dietary phosphorus intake to maintain serum phosphate levels in the normal range (18). Limiting processed foods with phosphorous-based additives and encouraging home-cooked meals from fresh ingredients (preferably plant-based foods) should be the first-line interventions for phosphorus restriction (31). As in the general population, vitamin D intake for CKD patients is recommended at 600–800 IU/day, but the optimal vitamin D levels in serum remain controversial (31, 32).

Low Protein Diet (LPD)

The benefits of LPDs include slowing the progression of CKD and reducing uremic symptoms and metabolic disorders (20, 21, 48, 49). Nearly 20 randomized controlled trials (RCTs) have assessed the effects of protein restriction on several renal outcomes, including CKD progression, proteinuria, phosphate levels, acidemia, and BP, which have been summarized in several meta-analyses and two Cochrane reviews (8–11, 15, 16, 50–56). Overall, the balance of evidence suggests a benefit of dietary protein restriction. The 2020 KDOQI guidelines recommend, in non-diabetic adults with CKD 3–5 who are metabolically stable, protein restriction for reducing the risk of progression to end-stage renal disease (ESRD) and death and improve quality of life. In adults with CKD 3–5 and who have diabetes, the guidelines suggest a higher protein intake up to 0.8–0.9 g/kg/day (18). For the study of the effect of LPD on survival,

they identified five RCTs. Three studies clearly indicated a beneficial effect of moderate restriction in dietary protein in the development of end stage renal disease (ESRD)/renal death (57–60), whereas two studies did not (61, 62). The results of the secondary analysis on the number of ESRD/renal death events combined from the three positive studies indicated a beneficial effect of protein restriction (OR 0.621; 95% CI: 0.391–0.985).

For the effect of LPD on quality of life, they identified a single RCT that demonstrated how the group with protein restriction presented significantly higher scores for general health and state physical compared to the control group (62). For the study of the effect of VLPD (very low protein diet) supplemented with AAEs and KAs, they reviewed a total of 13 RCTs and one non-RCT (63–76). The pooled analysis indicated a probable overall benefit of VLCD+KAs supplementation for the development of ESRD/renal death in patients with CKD stages 3–5 (RR 0.65; 95% CI: 0.49–0.85). After the 2020 K-DOQI guidelines, a new systematic review and meta-analysis explored the effectiveness and safety of VLCD supplemented with KAs compared to LPD or a normal protein diet in patients with CKD (15). Seventeen RCTs with a total of 1,459 patients were included. KAs-supplemented VLCD significantly conserved GFR and reduced proteinuria, phosphorus, and parathyroid hormone levels, systolic and diastolic BP, as well as serum cholesterol. Additionally, the analysis by subgroups showed how the VLPD supplemented with KAs was superior to the LPD with KA in the rate of decrease in GFR.

Animal vs. Plant-based Protein

Several observational studies have suggested that **plant proteins may have more reno-protective effects** than animal proteins. A diet rich in protein from plant sources may slow the progression of CKD (88–92), decrease proteinuria (93, 94), lower the level of uremic toxins (94–99), phosphorus intake, and the endogenous production of acid (89, 90, 100, 101). Moreover, such a diet could potentially improve survival (102). However, the confounding factors inherent in a diet rich in plant-based protein (i.e., higher intakes of vitamins and antioxidants) make it difficult to draw definite conclusions (103, 104).

Dietary Salt

Dietary sodium intake is a modifiable factor that can impact on the risk of CKD progression as well as on cardiovascular disease in CKD patients. Previous reports have demonstrated the effect of sodium intake on fluid overload and hypertension, both predictors of kidney progression and cardiovascular remodeling (105–109). In addition, high sodium intake might have direct toxic effects on blood vessels (109, 110). High salt intake is also a well-established risk factor for hypertension in KTR and can result in decreased graft survival (2, 111).

Conversely, salt restriction RCTs demonstrate a reduction in BP and proteinuria, with potential benefits on CKD progression and survival (5). A Cochrane review summarized the effects of salt restriction in CKD (8). Unfortunately, these studies did not show collectively a beneficial effect of a lower sodium intake on mortality, cardiovascular events, or CKD progression, probably due to their short follow-up and the limited sample size. It is interesting to highlight a significant decrease in proteinuria associated to a low salt diet, that was observed in all the RCTs that reported this outcome (112–115). The 2020 KDOQI guidelines recommend in adults with CKD 3–5, CKD 5D, or post-transplantation, a limitation in the sodium intake to <2.3 g/d (<100 mmol/d) to achieve a BP reduction, an improvement in volume control and a decrease in proteinuria levels (18). Nevertheless, the lack of long-term RCTs assessing the effectiveness and safety of dietary salt restriction on CKD progression and survival prevents any firm conclusions.

Reduced Phosphorus

Phosphate-specific diet therapy provided by a dietitian may reduce phosphate levels in CKD, although overall certainty of evidence is low (116). However, association between hyperphosphatemia and adverse cardiovascular outcomes and CKD progression is robust in this population (117–124), also in KTR (125–127). Altogether, it seems reasonable to recommend adjusting dietary phosphorus intake to maintain serum phosphate levels in the normal range (18, 105).

Dietary Patterns & CKD Progression

Historically, research recommendations and guidelines have focused primarily on modifying the single intake of micro or macronutrients (57). However, changes to eating habits remain minor, over time, for everyone, so that the overall dietary pattern may be more decisive for patients than an excess or deficiency in one specific nutrient (103). Adherence to healthy diet patterns as the Mediterranean and the DASH (The Dietary Approach to Stop Hypertension) diets has been linked to less rapid kidney function decline and favorable effects on cardiovascular morbidity and mortality in ND-CKD patients, including kidney transplant recipients (KTR) (140, 141). Plant-based diets could also mitigate metabolic acidosis in patients with CKD and potentially slow the progression of kidney disease, but evidence is limited (104). Conversely, a Western diet (rich in saturated fat, red and processed meat, and sweets) has been associated with an increased risk of CKD progression and albuminuria (142). The evidence is not conclusive as not all studies associate healthy dietary patterns and risk of ESRD (143). Collectively, there is a possibility that healthy dietary patterns may prevent the development of ESRD (5, 81, 146). Figure 8.2 is a schematic representation of reno-protective mechanisms related to protein and diet prescription, as well as synergy with pharmacologic approaches that target the renin-angiotensin system (RAS).

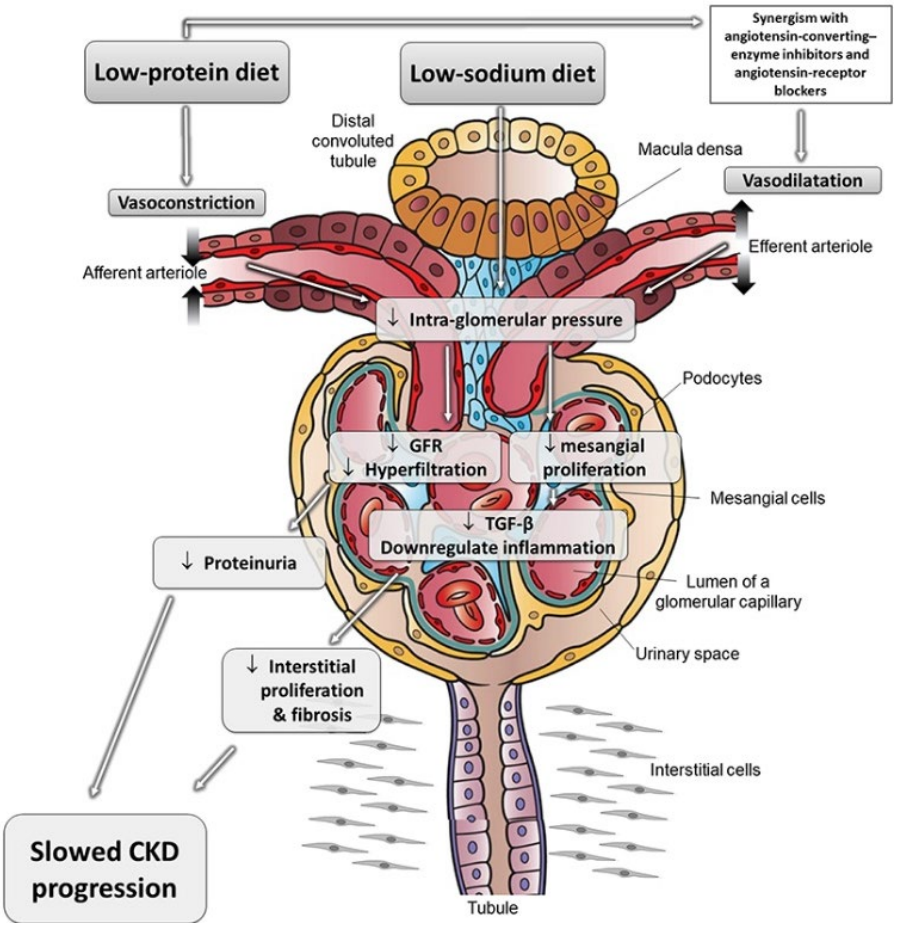

Figure 8.2 The effects of different nutritional interventions to slow progression of CKD.