Nutrition and Non-Insulin Dependent Diabetes Mellitus from an Anthropological Perspective

C. Leigh Broadhurst, Ph.D.

Abstract

Homo Sapiens is considered to be adapted to a Paleolithic hunter-gatherer diet, and was present in anatomically modern form more than 100,000 years before the adoption of agriculture. The causative factors for non-insulin dependent diabetes mellitus (NIDDM) relate to adopting Western dietary standards based on abundant, processed agricultural foods. Ethnic minorities adopting Western diets have uniform increases in NIDDM incidence, but there are also intrinsic differences in NIDDM incidence between various ethnic groups.

Insulin sensitivity correlates positively with membrane unsaturation and omega-3/omega-6 polyunsaturated fatty acids (PUFA) in phospholipids, and negatively with intramuscular triglyceride and central obesity. Omega-3 PUFA supplementation is recommended for NIDDM, including long-chain PUFA. Chromium (Cr) is required for normal insulin function; however, we require more Cr than is provided by the typical Western diet. Cr supplementation well above the Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 50-200 mcg/day may be required to prevent and treat NIDDM. In the past, Cr dietary availability is likely to have been higher, yet requirements lower.

In plant foods, many biologically active phytochemicals are bitter or astringent, so many plants have been bred to contain lower levels. Simultaneously, these food have become sweeter and less fibrous. Hence, consuming modern produce is not equivalent to consuming the wild precursors. Herbal products can provide these phytochemicals and fibers. Many botanical products have benefits for controlling diabetes beyond the inhibition of glucose absorption, including stimulating insulin secretion and/or action, improving insulin binding, improving capillary function, and preventing PUFA peroxidation.

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Introduction

Non-insulin dependent diabetes mellitus (NIDDM), or Type II diabetes is one of the largest health problems in Western countries. NIDDM currently affects some 6–12 million persons in the US, and incidence is increasing despite continual advances in medical care. Approximately

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95% of diabetics are Type II, presenting with symptoms well into adulthood. While there is some genetic propensity for development of NIDDM, the etiology of this disease is largely nutritional. The small number of genetic factors currently identified with NIDDM are likely to be factors which are expressed by current Western diets.[1-3] No genes particular to NIDDM have thus far been identified, but there are combinations of candidate genes which may confer a susceptibility toward glucose intolerance and insulin resistance.[4] However, these various genetic factors may not have led to NIDDM in the past or under other circumstances. It is crucial to understand that unlike Type I (insulin-dependent diabetes), NIDDM is almost entirely both caused and prevented by nutritional choices, thus it is amenable to holistic alternative medical treatment.

The incidence of diabetes in seven U.S. ethnic minorities (for which there are data) is much higher than the incidence in their respective countries of origin.[5] This indicates when these groups adopt Western eating and lifestyle practices, the incidence of NIDDM increases uniformly. This same epidemiological trend has long been recognized for cardiovascular disease and colon cancer.[6-9]

The U.S. diet provides the highest amount of calories for the lowest cost worldwide.[9] It also has the highest availability of large-scale agricultural commodities, and refined and processed food products. The U.S. diet is becoming popular around the world, but is also the diet farthest removed from that which *Homo sapiens* is considered to have evolved eating.[9-12] Broadhurst[13] proposed the following list, namely that the major causative factors for NIDDM, while exacerbated by aging, can all be related to a modern agricultural-processed food based diet:

1. Obesity and overfatness: In particular, simultaneously increasing lean body mass with resistance training while decreasing body fat provides significant improvement in glycemic control.
2. Carbohydrate (especially in refined and processed forms) and fat overnutrition.
3. Lack of polyunsaturated fatty acids (PUFA) in plasma membranes and unbalanced triglyceride intake.
4. Chromium deficiency.
5. Lack of soluble fiber and relevant beneficial phytochemicals.

Factors 1 and 2 have long been known and researched, and will not be reviewed here. Many of the included references provide extensive information on these factors. Obesity is the single largest cause of NIDDM, and overnutrition is the single largest cause of obesity.[14-17] Physical activity is known to improve both glucose tolerance and overfatness.[15,18,19] The benefits of diets based on unrefined whole foods versus refined foods have also been documented.[14,20,21] Factors 3-5 are not only independently significant but also synergistic, yet discussion of them is often lacking in protocols for diabetes management. Hence, they are the focus of this paper.

Paleolithic Requirements Define Our Nutritional Needs

A concept of overriding importance in human nutrition is that we still have the metabolisms and physiologies of Paleolithic hunter-gatherers. Based on the relatively slow pace of skeletal morphologic changes required to define a hominid genus,[22-25] our fundamental nutritional needs have probably changed little since the rise of our genus 2-2.5 million years ago. At a minimum, we are obliged to recognize our nutritional requirements cannot have changed significantly since the rise of our species *Homo sapiens* in Africa between 100,000 and 300,000 years ago.[24-28] Extensive discussion of this subject is beyond the present scope, but reviews of the role of nutrition in human evolution can be found in refs. 9 and 29-31.

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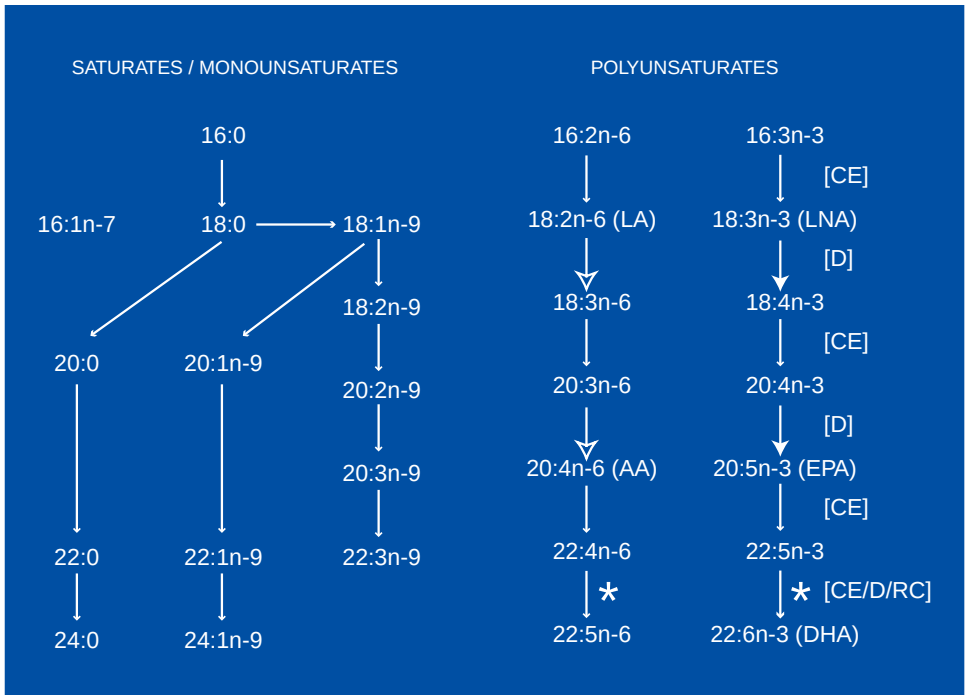
Figure 1. Long chain fatty acid pathways in mammals.



Palmitic acid (16:0) is the starting point for saturates (18:0 to 24:0) and monounsaturates (16: ln-7 through 24: ln-9). Linoleic acid (LA, 18:2n-6) and a-linolenic acid (LNA, 18:3n-3) are the main precursors to the polyunsaturates (n-3 and n-6 PUFA series). Note also that the 16 carbon n-6 and n-3 PUFA are present in the human diet *(i.e.* selected green vegetables) and can be metabolised to 18:2n-6 and 18:3n-3. Pathways proceed through chain elongation [CE] and desaturation [D]. The final step in PUFA metabolism involves retroconversion [RC] from 24-carbon intermediates [*] not shown. Preference by desaturase enzymes is shown by the arrowheads:

The remains of anatomically modern humans *H. sapiens* (var. sapiens or proto-Cro-Magnon) dating to prior to 100,000 years ago have been found in localities in southern Europe and the Middle East, and modern humans were widespread across Eurasia by 40,000 years ago.[26,32,33] This is a very long time as compared to the 10,000 years since the initial adoption of agriculture, and the 50-100 years that modern processed foods have been available. For 99.8% of our time as genus *Homo* we ate exclusively wild foods.[9,11,12] As far as human evolution and metabolism is concerned, agriculture is a new experience — we are still in the initial stages of a grand experiment conducted on ourselves. Logic dictates we must at least consider that the profound changes in our diets since the Neolithic Revolution have a role in the origin of NIDDM.

Basic Composition Of Hunter-Gatherer Diets

Archeological and ethnological studies have evaluated the composition of hunter-gatherer diets in both prehistoric and historic/existing populations. Preagricultural diets are/were dependent on animal protein and fat, and wild vegetation.[10,11] With the rare exception of honey, they never contained concentrated carbohydrate sources such as sugar, flour, rice, and pasta. In temperate and especially colder climates, carbohydrates were exceedingly limited. In the extreme, traditional diets of Arctic societies are virtually devoid of carbohydrate.[34-37] Similarly, North American Northwest coast Indians traditionally consumed great quantities of fat because carbohydrate was limited to scarce clover roots and a short berry season.[38] Tropical and subtropical environments provided consistently higher amount of fruits, honey, and starchy roots and tubers; however, fat and protein-rich nuts often provided the largest percentage of calories from plant foods[34,39] Cereal grains were unknown, as were legumes such as soybeans and kidney beans. In some environments, legumes may have been consumed in their green state; however, dried mature beans were only occasionally utilized. Like cereal grains, mature legumes such as soybeans require commercial agricultural production, and are also totally inedible unless cooked. In addition, many wild legumes are toxic.[40, 41]

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Based on ethnographic observations of extant populations as well as archaeological evidence, hunter-gatherers used game, fish, shellfish, reptiles, amphibians, and insects for protein sources. On average, total dietary fat in the hunter-gatherer diet is not considered to have exceeded 30%en (less than 30% of the total caloric intake as fat); however, diets were never fat-free, and as mentioned above, some groups ate considerable fat. Cross-cultural ethnographic and historical studies have repeatedly observed that great efforts are made to seek out and consume animal protein and fat.[35,42,43] In general, edible portions of wild game, fish, and shellfish contain a greater percentage of structural fat and protein and less storage fat per unit weight than does meat from livestock.[44,45] Structural fat is typically more roughly balanced in polyunsaturated fatty acids (PUFA, including long-chain or LC-PUFA), mono-unsaturated fatty acids (MUFA), and saturated fatty acids (SFA) than is storage fat.[46,47] Storage fat usually has a higher percentage of SFA, and meats with a good deal of intramuscular fat (marbling) have both higher absolute and relative amounts of SFA per unit weight than do lean meats.

PUFA Balance And Membrane Abnormalities

Abnormal membrane phospholipid profiles is of major significance in both Type I and Type II diabetes.[48-50] It is known that insulin stimulates and glucagon inhibits the desaturase enzyme system (Fig. 1), thus influencing the PUFA available for membrane incorporation. Conversely, the fatty acid composition of membrane lipids influences the action of insulin. Experimental data have shown that increasing membrane fluidity by feeding higher dietary levels of PUFA increases the number of insulin receptors, therefore increasing insulin activity. In humans with Type I diabetes, and in chemically-induced diabetic animal models, insulin administration and LC-PUFA supplementation (*i.e.*, evening primrose and fish oils) can partially correct the membrane abnormalities.[50,51] However, most diabetics are Type II, characterized by hyperinsulinemia or insulin resistance. Roughly 75% of Type II diabetics have elevated levels of insulin, but this insulin is not totally effective.[52] Type II diabetic membrane abnormalities thus cannot be only the result of insulin/glucagon influences on the desaturase system; rather, the diabetic condition may result from accumulating membrane abnormalities.

A recent study comparing 575 diabetics (242 IDDM and 333 NIDDM subjects) with 319 normal controls showed a failure to incorporate PUFA in cell membranes is a broad characteristic of human diabetes.[53] All diabetic red cell membranes were relatively lower in PUFA, with a concomitant increase in MUFA and SFA. In IDDM patients, linoleic acid (LA) was elevated relative to its metabolites (see Fig. 1) in red cell and plasma phospholipids, triglycerides, and cholesterol esters, consistent with a simple impairment of PUFA metabolism. NIDDM patients had a normal ratio of plasma phospholipids, and elevated LA in red cell phospholipids, cholesterol esters, and triglyceride, although not to the degree seen in the IDDM patients. This again indicates that in NIDDM impaired insulin activity may be both a cause and an effect of membrane PUFA composition.

Omega-6 and Omega-3 PUFA Balance

Intensive research during the past 15 years has firmly concluded the n-6 to n-3 PUFA ratio in the current Western diet is much higher than is recommended.[54,55] Due mainly to the prevalence of agricultural oils such as corn, soybean, sunflower, peanut, and cottonseed, LA is normally greater than 85% of total dietary PUFA.[56] N-3 intake is further reduced by an estimated average intake of 13.3 gm/

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person/day *trans*-fats in the United States.[57] This figure may be even higher, based on new analytical techniques.[58] Huang and Nassar,[59] Lands et al,[60] and Broadhurst[13] reviewed dietary PUFA, and concluded n-6 and n-3 fatty acids must be considered together, and must be balanced in the diet. Dietary PUFA balance is necessary because n-6 and n-3 PUFA compete for the same desaturase and elongase enzymes (Fig. 1). Too much n-6 inhibits desaturation (and to a lesser degree elongation) of n-3, and vice versa. In addition, Δ5 and Δ6 desaturase activity is regulated by a number of factors, including insulin activity.[50,61,62] Current Western dietary guidelines for the overall ratio in dietary n-6 to n-3 PUFA are 5-10:1[63] and 4:1.[64] Ratios of 4:1 to 1:1 are advocated by many researchers who have examined the fatty acid composition of mammalian organ and neural tissues, and traditional hunter-gatherer foods.[30,31,44-46,65-67] Our current high intake of n-6 PUFA (especially LA), with n-6 to n-3 ratios on the order of 15 to 45, is unprecedented in human history and prehistory.

Lipid nutrition, muscle membrane function, and insulin efficiency

Diets relatively high in SFA, hydrogenated fat, and n-6 PUFA can significantly affect insulin efficiency and glucose response. Skeletal muscle is the major site of insulin-stimulated glucose utilization.[(footnote a)] High fat diets increase the accumulation of storage triglyceride in skeletal muscles (*i.e.*,"marbling"), which leads directly to insulin resistance in the individual muscles.[2,68] When a percentage of n-3 PUFA is substituted for other fat in the diets of rats or humans, insulin resistance can be improved or prevented.[2,68,69] The fat composition of muscle membrane phospholipids reflects the combined influences of diet and desaturase/elongase activity, and in turn the phospholipid composition affects the binding and action of insulin. In general, the more the unsaturated (flexible; fluid) the membrane, the better glucose is utilized. The more saturated the membrane, the more deleterious the effect on insulin efficiency.[68,70] This does not mean NIDDM *cannot* develop if membrane fluidity is normal, but rather that PUFA metabolism has a greater or lesser role in NIDDM depending on an individual's diet and genetics.[71]

For example, insulin-stimulated glucose metabolism was low in genetically obese rats fed a high fat, n-3 deficient diet, but returned to normal when n-3 LC-PUFA (fish oil) was added to the diet. The rats' metabolic rate also increased significantly.[72] Similar results were seen in streptozotocin-induced diabetic rats on high fat diets, where higher ratios of PUFA to SFA in various diet groups was associated with improved insulin binding.[61] Normal rats fed high fat diets all became insulin resistant with high SFA, MUFA, and LA diets, with SFA causing the most deterioration and LA causing the least.[49] Substituting 11% of fat with n-3 LC-PUFA from fish oil completely normalized insulin function. A similar replacement with n-3 as alpha-linolenic acid (LNA) from flaxseed oil normalized insulin function in the SFA diet group, but was ineffective in the LA group.

Results from adult human studies are consistent with those from rodents. In three different studies, (Caucasian Australian, Caucasian Swedish, Arizona Pima Indians) muscle biopsies obtained during surgery were correlated with fasting glucose or euglycemic clamp tests. In all studies, the higher the degree of membrane saturation, the more insulin-resistant the individual.[68,69] Both hyperglycemic and normoglycemic individuals were studied.

Earlier concerns that fish oil supplementation might cause elevated glucose levels in diabetics, purportedly by reducing insulin secretion, have not been confirmed by

[a] Different types of muscle fibers also differ in their insulin sensitivity, with type I (slow twitch oxidative) and to a lesser extent type IIa (fast twitch oxidative) more sensitive than type IIb (fast twitch glycolitic).[73,74]

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recent research.[69,75] Sirtori et al conducted a large (n=935), multi-center, double-blind study on hypertrigylceridemic subjects, and found plasma triacylglycerol decreased up to 21.5% with modest supplementation of n-3 LC-PUFA as ethyl esters.[75] In addition to hypertriglyceridemia, 55% of subjects had NIDDM or impaired glucose tolerance, and 68% had arterial hypertension. Subjects were given 1530 mg EPA and 1050 mg DHA daily for two months, then decreased to 1020 mg EPA and 700 mg DHA daily for the following four months. Placebo subjects received olive oil. No effects on glycemic control or blood pressure were recorded, and those with NIDDM had proportionally greater decreases in triacylglycerols and increases in HDL cholesterol.

It is important to make the distinction between fat either stored or used as a substrate for energy metabolism, and structural fat — most importantly the structural fat contained in the cell membranes of insulin-sensitive tissues. Provided energy balance is maintained, high MUFA diets have shown the potential to be broadly beneficial for diabetics, especially if monoenes are substituted isocalorically for carbohydrates or SFA.[17,76-78] In these cases, MUFA is provided for energy, and the underlying assumption is that structural PUFA are not deficient. This contrasts with the rodent studies above (and other such studies), where the animals are purposely raised to be PUFA-deficient. The imposition of PUFA deficiency is not ethical for human experimentation, but possible nonetheless through self-imposed dietary choices. The question relating to the fat content of hunter-gatherer diets and the origin of NIDDM is not simply: "Which dietary fats can best ameliorate existing diabetes?" but more importantly: "Is the profound loss of n-3 LC-PUFA and/or imbalance in triglyceride types in the current Western diet a potentially preventable *cause* of NIDDM?"

In the latter case we must consider the potential effects on *structural fat* of a lifetime of consuming dietary fats composed mainly of SFA, LA, and *trans*-fats. It is interesting to note that in a crossover diet study, Christiansen et al found that *trans*-monoenes were not beneficial for diabetics.[78] Sixteen obese NIDDM patients were fed 20%en of either *trans*-MUFA, *cis*-MUFA, (*i.e.*, oleic acid), or SFA in a diet with 30%en from fat overall, with 6 weeks for each diet type. Both SFA and *trans*-MUFA increased postprandial insulin and C-peptide secretion, but *cis*-MUFA had no effect. Serum glucose and lipids were not significantly different in any of the groups, which may indicate reduced insulin sensitivity in the SFA and *trans*-MUFA groups.

PUFA balance, central obesity, and insulin efficiency

Central obesity is associated with a high incidence of NIDDM as well as cardiovascular disease, hypertension, and premature mortality. Abdominally-obese individuals tend to have a diminished capability to utilize glucose peripherally, or extract insulin during its first portal passage. They also have increased circulating free fatty acids (which reduces glucose metabolism), and a decline in insulin receptor number.[79] Two populations prone to central obesity, Arizona Pima Indians [80,81] and South Asian Indians,[82] appear to have a genetic predisposition for NIDDM. However, it is acknowledged that widespread health problems did not arise until these populations adopted Western food shopping and dietary habits. According to Szathmary,[3] NIDDM was virtually unknown in North American aboriginal populations before 1940.

Dramatic increases in calories, refined carbohydrates, total fat, and n-6/n-3 PUFA ratios have affected these populations. In both the Australian and Pima subjects above, increasing n-6/n-3 ratios correlated positively with obesity and insulin resistance. However, the Pimas had much lower n-3 PUFA in their membrane phospholipids than Australian or

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especially Swedish subjects.[81] In the case of the Australians versus the Pima, Pan et al found little evidence for greatly differing dietary intakes; however, the average docosahexaenoic acid (DHA) content of muscle phospholipids was 2.5±0.7% versus 1.2±0.1%, respectively.[2]

This situation for the native American population overall probably reflects both decreased dietary intake and decreased desaturase/elongase activity. In the Pima studied by Pan et al,[2] both impaired insulin action and obesity were found to be independently related to reduced Δ5 desaturase activity. Vancouver Island Canadian natives and Greenland Eskimos, closed-society groups accustomed to traditional marine diets, have been shown to have a limited ability to convert 18-carbon PUFA to LC-PUFA, which is likely to be genetic.[83] The overall incidence of NIDDM in the Pima is the highest of any ethnic group known (50%), and specific genetic factors may play a role. For example, the Pima exhibit a small intestine fatty acid binding protein genotype that increases the affinity of that protein for long-chain fatty acids. This increase in affinity may increase the transport of fats across the intestine. This genotype is also associated with higher mean fasting glucose levels, and greater insulin responses to both oral glucose and mixed meals.[84] Especially disturbing is the observation that Pima mothers who were diabetic during pregnancy have children with a greater incidence of obesity and diabetes.[5]

South Asians living in the UK have a higher incidence of diabetes than the European Caucasian population (19% versus 4%), and a significantly greater age-standardized coronary heart disease mortality. While South Asians are no more overweight than their European counterparts, the former have a marked tendency towards central obesity.[82,85] The diet of South Asians has a much greater ratio of PUFA to SFA than the typical Western diet; however, the n-6/n-3 ratio is very high. Das found elevated lipid peroxides and decreased plasma PUFA metabolites in 10 moderate NIDDM (no complications) and 10 severe NIDDM (unequivocal nephropathy) subjects as compared to 20 controls.[85] Lipid peroxidation was confirmed by the plasma malondialdehyde equivalents for the three groups: 2.4±0.6, 3.0±1.1, and 1.27±0.23, respectively. Both groups of diabetics had significant reductions in dihomo gamma linolenic acid and arachidonic acid from the n-6 series, and LNA and DHA from the n-3 series (see Fig. 1). This also probably reflects a combination of decreased dietary LC-PUFA and n-3 PUFA intake coupled with reduced desaturase/elongase activity. In addition, the observed high levels of peroxidation in the diabetics may indicate destruction of PUFA as opposed to utilization.

A tendency to store fat, release insulin, and desaturate/elongate only the minimum amount of dietary 18-carbon PUFA metabolically necessary were likely positive factors for humans adapted to Paleolithic foods and constant physical activity, but might be maladaptive today. These are adaptations to a diet (a) low in fat and often energy, (b) relatively high in n-3 PUFA, (c) raw and unprocessed, and (d) free from high density carbohydrates — often such that dietary fat rather than carbohydrate was an absolute requirement for energy. The incidence of NIDDM in the U.S. is greater among minorities (Asian, Black, Hispanic, Native American) than Caucasians, even when diet and lifestyle factors are taken into account.[5] In addition, the incidence of NIDDM among Africans, Mexicans, Puerto Ricans, Koreans, Japanese, Chinese, and Filipinos (groups for which adequate data exist) residing in the U.S. is greater than the incidence in their respective countries of origin.[5] A widely accepted explanation for these observations is genetic "thriftiness," or a prevalence of genotypes which are adapted to sporadic wild food supplies and heavy physical

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labor.[3,86,87] As a group, Caucasians have most likely spent the longest time on an agricultural diet, and do tend to metabolize alcohol,[88] dairy products,[15,89] wheat and other glutinous grains,[90,91] and evidently sugars [5] better than other groups.[(footnote b)] Under equivalent dietary and environmental conditions, these adaptations may afford some protection from NIDDM, but are certainly not a panacea.

Native Americans are considered to have descended from a small group of individuals who crossed the Bering Land Bridge between 11,000 and 14,000 years ago.[92-94,(footnote c)] American Indians, regardless of where they live in the Americas, have more in common genetically with high-latitude Eskimo hunters than they do Caucasian Americans. Native Americans have also tended to remain in closed tribal societies, and many were still hunter-gatherers 100 years ago, thus modern agriculture, processed foods, and alcohol have been especially detrimental to their health.[43] Hispanics have mixed Caucasian and Native Latin American ancestry, and have an incidence of NIDDM between these two groups.[5] In the Western quest to "eat as much as you want and not gain weight" it is often forgotten that the evolutionary purpose for overeating *is* to gain weight, and to a greater or lesser degree, we are all adapted to do so, or we would never have survived in the past. Our ancestors gained weight voluntarily and lost it involuntarily, the exact opposite of what many of us attempt to do today.

In summary, both the quantity and type of fat ingested influence insulin sensitivity. Since skeletal muscle is the largest sink for glucose disposal, maintaining a high lean/fat tissue ratio is an overall recommendation for NIDDM prevention and management. In addition, reducing SFA and n-6 PUFA, while increasing n-3 PUFA is recommended. At least some n-3 should be from n-3 LC-PUFA, since there is variation in PUFA intake and metabolism among populations, and some groups with high NIDDM incidence appear to have a diminished capability to convert 18-carbon PUFA to LC-PUFA.

Chromium Nutrition

Chromium (Cr) deficiency is a causative factor for NIDDM, producing symptoms including fasting hyperglycemia, impaired glucose tolerance, decreased insulin binding and receptor number, decreased HDL, and increased total cholesterol and triglycerides.[52,95] A diet high in refined grains and sugars exacerbates Cr depletion. Firstly, these foods contain low amounts of Cr, yet Cr is necessary to metabolize them. Secondly, a high consumption of sugars and insulinogenic foods increases Cr urinary excretion by 10–300%.[96,97] Typical Western diets require more Cr than they provide, thus leading to long-term depletion of body Cr reserves. It is estimated the majority of the U.S. population does not obtain the Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 50–200 mcg/day Cr. Similar results have been observed in Canada, the UK, and Finland.[52,102,103]

In rats, Cr is stored mainly in the kidney, and to an order of magnitude less the liver, spleen, lungs, and heart. Plasma Cr is not in equilibrium with tissue stores.[104] Tissue stores are depleted by inadequate intake or absorption, pregnancy, strenuous exercise, a high intake of refined carbohydrates and processed foods, increasing age, infections, and trauma.[52,95] Exercise increases the metabolic rate; insulin receptors in the muscle cells are activated and glucose uptake is greatly enhanced over basal levels. This uptake requires

[b] In addition, regular alcohol consumption and chronic gastrointestinal inflammation, such as occurs in delayed-onset food allergies (common for wheat and some other grains, eggs, and dairy products), are associated with decreased desaturase activities, and impaired absorption and metabolism of PUFA, which may further exacerbate membrane abnormalities and increase the risk for NIDDM.[65, 98-100]

[c] Recently, the scanty evidence for entry prior to 50,000 years,[25, 94, 101] most of which comes from a site at Monte Verde, Chile, was officially acknowledged by the paleoanthropological community at large.

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concomitant action by Cr; however, it does not appear that Cr is efficiently recycled by the body. Urinary chromium excretion increases significantly following exercise.[105] Increased circulating insulin increases Cr urinary losses,[97] but also increases the body's requirements for Cr. Without Cr supplementation or dietary changes, hyperinsulinemia and glucose tolerance get progressively worse with time, and can eventually result in NIDDM.[103]

Chromium Absorption and Availability: Past and Present

Brewer's yeast, beer, whole grains, cheese, liver, and meat can be good dietary sources of Cr; however, Cr content of foods varies widely, and much of what is measured may be contamination from stainless steel processing equipment. Refining of grains and sugars, and processing of foods removes most of the absorbable Cr.[95,102] Unlike most essential trace elements, Cr has not been shown to be essential for major agricultural plants,[106,107] thus Cr levels depend simply on how and where various plants are grown. Accordingly, fruits, vegetables, grains, and legumes intrinsically contain varying amounts of Cr. Soils with abundant Cr must of necessity develop from underlying rocks rich in Cr.

It is a fundamental principle of geochemistry that rocks rich in Cr [(footnote d)] are common in the Earth's mantle and to a lesser extent in the oceanic crust, but are rare in the continental crust.[108-110] Cr-rich rocks found on the continents are restricted to exposed areas in which pieces of oceanic crust and/or mantle have been pushed up onto the continents. This type of activity is observed only at geologically active plate margins where one plate is thrust beneath another (known as subduction zones), or where plates have rifted and new oceanic crust is being created. Currently, these active plate margins are found along ocean coastlines, thus Cr-rich rocks are confined to areas which are now or were once geologically active coasts or ocean basins. The Peru-Chile subduction trench and associated Andes mountains along the west coast of South America is a current example of such a coast. The Great Valley of California is explained geologically as having been a subduction trench *circa* 65 million years ago.[111] Its fertile, Cr-rich [112] soil is the legacy we have today.

In humans, Cr absorption is regulated and inversely related to dietary intake at levels <40 mg. Above 40 mg, absorption appears to remain constant. Inorganic forms of Cr are very poorly absorbed (<1%). Organic Cr complexes have better absorption than inorganic salts, but the levels of absorption are still below 10%.[104] The biologically active form of Cr appears to be a nicotinic acid-amino acid complex, and Cr is not effective if nicotinic acid is deficient.[114] This does not mean, however, that Cr nicotinic acid complexes are the necessary or preferred type of Cr nutritional supplementation; on the contrary they appear to be more poorly absorbed than Cr picolinate or chromium-rich yeast extracts.[104,115] Broadhurst et al[115] showed that in Cr "polynicotinate" Cr is not bonded to nicotinic acid, but rather to OH and/or H_2O in an olate structure. Further, the amount of nicotinic acid in a typical 200 mg Cr supplement is quantitatively insignificant with respect to the RDA of 18 mg, and especially with respect to the approximately 100 mg necessary to reverse niacin deficiency. Cr and nicotinic acid supplements administered independently have been shown to improve glucose tolerance while either component alone was ineffective.[114]

[d] This applies to cobalt, nickel, and platinum group elements as well. The richest deposits by far of all these metals are found in unusual deposits where ancient (1–3.8 billion year-old) mantle-derived rocks have been exposed by deep erosion, but not destroyed by more recent geologic activity. The mineral deposits of South Africa are the best example of this.[113] The Earth was much hotter then, and plate tectonic cycles which may have been present must have differed considerably from that of the past billion years. Hence, there are no comparatively recent examples of such high-concentration metal ores.

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Appropriate dietary choices and supplementation of Cr on the order of 200–400 mcg/day may help prevent NIDDM, but may not be sufficient to reverse existing diabetes. A recent double-blind study on three groups of 60 Chinese Type II diabetics found that 500 mcg Cr (as chromium picolinate) given twice per day for four months was greatly superior to placebo at lowering fasting glucose (129 mg/dL versus 160 mg/dL), 2-hr postprandial glucose tolerance (190 mg/dL versus 223 mg/dL) and nearly normalizing glycosylated hemoglobin (6.6±0.1% versus 8.5±0.2%). Plasma total cholesterol and circulating insulin also dropped. A third group given 100 mcg twice per day showed lesser but significant improvements in glycosylated hemoglobin and insulin levels, but not blood glucose.[116]

If Cr is so poorly absorbed and sporadically distributed, it is reasonable to ask how humans could have existed in the past without developing Cr deficiencies. Perhaps many did — we can never know for sure, but our ancestors had two points on their side. Firstly, their Cr needs were almost certainly lower because they consumed no cereal grains or refined sugars, but did consume lean free-living game, fish etc., more balanced PUFA, soluble fiber, and wild vegetation (discussion follows). In addition, ethnographic observations show that traditional hunters make a point to consume the brains, organs, and bone marrow of game and fish,[35,45,117,118] which are rich sources of many trace elements, Cr included.[104] We have no reason to think this was different in the past: archaeological investigations of Paleolithic scavenging/kill sites reveal efficient butchering techniques and evidence of skull and bone crushing.[93,117,119,120] In fact, a feature of the U.S. diet is its almost exclusive reliance on muscle meats.

Secondly, based on a continuous record of hominid fossils,[26,32] our earliest ancestors lived in the East African Rift Valley for over for 4 million years, and the Rift Valley is an environment with abundant Cr in the rocks and soils. Soils and rocks in the Rift Valley are relatively rich in *all* trace minerals due the constant geologic activity.[121] The African Rift, the Red Sea, and the Gulf of Aden together form our only current example of what is termed geologically a "failed ocean." Extensive geologic investigation has concluded that starting 30 million years ago, the Arabian peninsula moved slightly away from Africa, but has now nearly stopped.[122] Even a novice observer can gain an understanding of the plate tectonics of the Arabian peninsula and the East African Rift Valley by simple examination of a map or aerial photograph of the area. Throughout the evolution of hominids, volcanoes erupted constantly, covering the area with trace-element rich lava and ash.[121,123] Enormous lakes filled the linked fault basins which collectively form the Rift axis. These lakes are in fact "proto-oceans", in terms of their size, geologic origin, and very high levels of dissolved minerals.[31]

The weight of evidence from archaeology, hominid phylogeny, and mitochondrial DNA studies points to a single speciation event *circa* 100,000–300,000 years ago in Africa which produced *Homo sapiens* .[26,27,31,124,125 (footnote e)] *H. sapiens* populations then migrated out of Africa to the rest of the world, rather than independent coevolution of separate populations of precursor *H. sapiens* species. After migration, a number of nutritional, social, and economic factors confined most of the human population to coastal environments, and in fact the majority of the world's population is still confined to the coast .[9,30] Adoption of agriculture, as well as large-scale migration into interior areas, are thought to be recent phenomena, linked to the

[e] In addition, a very young date of 27-53 kyr for *H. erectus* in Java was recently reported.[129] If confirmed, this would require coexistence of *H. erectus*, *H. neanderthalensis*, and *H. sapiens* ,and would preclude independent evolution of disparate *H. erectus* populations into *H. sapiens.*

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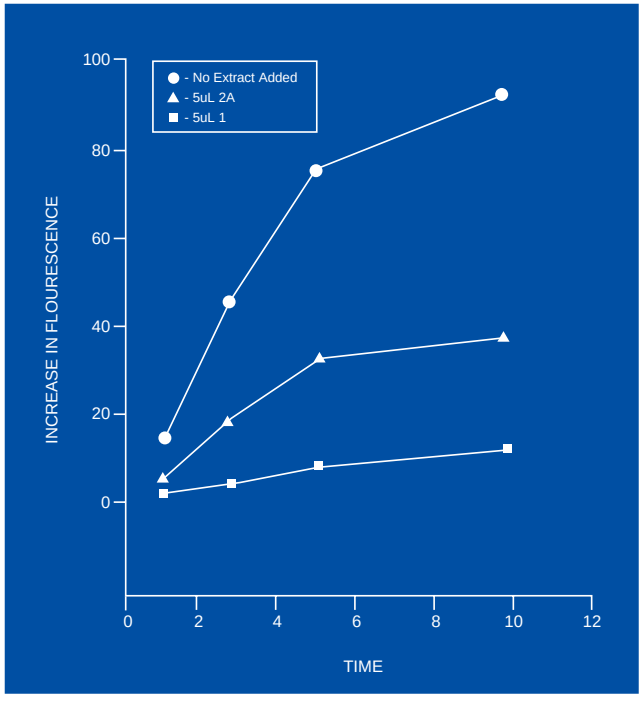
Figure 2. Inhibition of production of reactive oxygen species in platelets by methlyl-hydroxy chalcone polymer (MHCP).



Whole blood is incubated with 10 uM 2'7'- dichlorodihydrofluorescein diacetate for 10 min, followed by a 5 min exposure to MHCP solution or vehicle control. Collagen at 20 uglmi is added, and platelets in the samples are monitored for increases in fluorescence by flow cytometry at times indicated. Platelets are known to produce hydrogen peroxide, particularly when collagen is used to stimulate them. MHCP 1 is 1 mg/mi, and is likely to be a slightly lower molecular weight than MHCP 2A (4.5 mg/mi). The data show a significant, dose-dependent decrease in fluorescence with MCHP treatment.

recession of continental glaciers 10,000 years ago (*i.e.*, the end of the most recent Ice Age).[37,88,90] Coastal areas are generally richer in all trace elements, especially Cr, Se, and I — the three trace elements that mammals need but plants do not.

In summary, both Cr and PUFA deficiencies and/or metabolic abnormalities increase with increasing %en from fat, intake of refined and processed foods, and age. Like balanced PUFA intakes, Cr improves insulin action and plasma lipid profiles; however, the exact mechanisms are not elucidated. Nutritional and geologic/evolutionary factors have seemingly conspired to produce widespread Cr deficiencies. Therefore, supplementation of Cr well above ESADDI levels may be necessary to both treat and prevent NIDDM.

Very recent research has shown that Cr supplementation can improve insulin resistance induced in rats by feeding a high fat diet. .[126] It is plausible there is a specific relationship between the actions of PUFA and Cr with respect to plasma membranes; in any case, supplementation with both Cr and n-3 PUFA may provide synergistic benefits on glucose metabolism and serum lipid profiles.

Phytochemical Influences

Pharmacologically active plant phytochemicals include flavonoids, saponins, lignans, and tannins. Many of these compounds are bitter or astringent; therefore horticulturists have selectively bred these compounds down to low levels, or concentrated them in peels, which are often not consumed.[40,127,128] Produce is consistently bred to be larger, sweeter, and milder. The fruit and vegetables our Paleolithic ancestors ate were more akin to chickweed, choke cherries, and kumquats than iceberg lettuce, bing cherries, or navel oranges. Consequently, we may have lost a good deal of phytochemical protection from many pathologies, NIDDM included. The more bland and processed the diet, the greater the loss. The strong-tasting vegetable kale, for example, had the highest antioxidant capacity of 21 vegetables studied,[130] which is not surprising since wild kale is the precursor to all *Brassica* species, from kolrhabi to cabbage to cauliflower. Kale bears the most similarity to the Brassicas we evolved eating.

Evolutionary perspectives aside, most of us are not going to return to a diet of the bitter, fibrous, "edible weeds," the wild precursors to modern cultivated produce. However, many of the aforementioned bitter and astringent phytochemicals are present today in herbal products. The use of medicinal plants for diabetes is not just a search for safer alternatives to pharmaceuticals which transiently lower blood glucose. Rather, we gain insight into the validity of traditional tonic and adaptogenic herbs and foods. Herbal products

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can return valuable components to the diet, thereby making it more similar to our evolutionary diet with minimal effort.

According to Marles and Farnsworth,[131] 1,123 plants have been used to treat diabetes. Of 295 traditionally used plants screened *in vitro*, 81% were potentially antidiabetic. Over 200 pure phytochemicals are known to be hypoglycemic. However, Marles and Farnsworth[131] caution that 1/3 to 2/3 of the 1,123 plants may be dangerous, and many of the phytochemicals are hypoglycemic due to metabolic or hepatic toxicity. Conversely, there are hypoglycemic plants which are safe and effective *precisely because* they help return us to our evolutionary diet. The following subsections discuss plants which have clinical studies confirming efficacy.

Actions of Phytochemicals

In some cases, plant phytochemicals can directly stimulate insulin secretion and/or action, and improve insulin action and binding. Common spices such as cinnamon, cloves, and bay leaf have demonstrated insulin potentiating action *in vitro* .[132] It was thought that these spices might have high Cr concentrations, but measurements showed no correlation between Cr content and insulin activity. Cinnamon was particularly active, so we focused on it. From an extract of commercial cinnamon, a novel methylhydroxy chalcone polymer (MHCP) was identified which increases glucose metabolism of the cells 20-fold *in vitro* in the epididymal fat cell assay .[128] Over 40 plant extracts have been investigated in this assay, including many mentioned herein; however, none have shown activity near that of cinnamon (R. A. Anderson, C. L. Broadhurst, M. M. Polansky, in preparation).

Botanicals demonstrating *in vivo* hypoglycemic activity in animals include juniper berries,[133] izui,[134] Siberian ginseng, ganoderma mushroom,[135] cumin, cucumber, and bottle gourd.[136] Table 1 lists some of the more promising hypoglycemic plants which have not yet been adequately clinically tested.

Since insulin action has been positively correlated with skeletal muscle capillary density,[73] phytochemicals which can improve skeletal muscle capillary function have the potential to directly improve insulin action. Examples of herbal products which have been shown to improve capillary function are horse

Table 1. Promising botanical treatments for NIDDM, based on *in vitro* or *in vivo* animal studies. References cited, or can be found in Bailey and Day (1989), Marles and Farnsworth (1994), Broadhurst (1997), or Duke et al. (1997).

Common Name	Latin Binomial
Cloves	Syzygium aromaticum
Cinnamon	Cinnamomum spp.
Turmeric	Curcuma longa[a]
Bay leaf	Laurus nobilis
Black walnut	Juglans regia
Juniper berries	Juniperus communis
Izui	Polygonatum officinale
Syrian Christ thorne	Zizyphus spina-christi
Guduchi	Tinospora cordifolia, T. crispa
Cumin	Cuminum cyminum
Black cumin	Nigella sativa
Cucumber	Cucumus sativa
Bottle gourd	Curcubita ficifolia
Goat's rue	Galega officinalis[b]
Ganoderma mushroom	Ganoderma lucidum
Java plum	Syzygium jambolanum
Siberian ginseng	Eleutherococcus senticosus
Coriander	Coriandrum sativum
Sage	Salvia spp.

a. Based mainly on antioxidant properties.
b. *G. officinalis* has been tested in humans and can be effective, but is not considered generally safe. It contains the guanadine derivative galegin, which is similar to synthetic pharmaceutical hypoglycemic biguanides

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chestnut, bilberry, ginkgo, *Centella asiatica*, and various standardized anthocyanin preparations.[40,137-139] Bilberry in particular has been shown to improve edema and microangiopathy in diabetics.[138,140]

Modest buckwheat, butcher's broom, and hydroxyethyl rutoside supplementation significantly regressed diabetic retinopathy in humans, probably due to improved local circulation in the retina.[141] These three treatments also lowered total cholesterol and triglycerides, and raised HDL cholesterol. Cinnamon also contains procyanidin dimers and oligomers of the type thought to improve capillary function.[142]

Botanical antioxidants can play a role in NIDDM, helping maintain the integrity of cell membranes by preventing PUFA peroxidation. As discussed above, membrane unsaturation correlates positively with insulin function. Many botanical antioxidants (*e.g.*, cloves, cumin, cinnamon, curcumin, rosemary, many mint family plants, and various bioflavonoid preparations[40,143)] are both powerful and synergistic with antioxidant vitamins. Lipid peroxidation and damage by reactive oxygen species are also major problems in terms of diabetic complications. The MHCP extract from cinnamon strongly inhibits the formation of reactive oxygen species in collagen-activated platelets *in vitro* (Fig. 2), so may provide synergistic benefits. In addition, some phytochemicals directly influence the PUFA desaturase system and arachidonic acid metabolism.[40,128,144]

Traditional Tonic Plants: Human studies

Four traditional plants have clinical studies which document their efficacy:

1. Bitter melon *(Momordica charantia).* Unripe bitter melon is used traditionally in India, Africa, and Asia as a diabetic remedy and bitter tonic food. Bitter melon contains a nonpurified mix of hypoglycemic compounds ("charatin"), and an insulin-like protein. The effects of bitter melon are gradual and cumulative, and a juice or decoction is more effective than the powdered dried preparation.[145] Srivastava et al[145] gave 6 Type II diabetics 100 ml/day of a bitter melon decoction. After three weeks, their fasting blood glucose dropped by 54%. After seven weeks, all six were at or near the normal glucose limit, urinary sugar was no longer detectable, and glycosylated hemoglobin dropped nearly 2 mg%.
2. Gurmar *(Gymnema sylvestre).* The leaves of this climbing vine are an ancient Ayurvedic treatment for diabetes.[146] Gurmar appears to stimulate insulin secretion and lower cholesterol and triglycerides without side-effects.[147,148] In an open study, 22 NIDDM patients on oral antihyperglycemics were given 400 mg/day of a standardized extract for 18–20 months. All 22 were able to reduce their medication, and five were able to discontinue it. The extract was judged superior to prescription medication for long-term blood glucose stabilization, lowering of triglycerides, and the overall well-being of the patients.[149,(footnote f)]
3. Korean ginseng *(Panax ginsen*g). Traditional Chinese medicine recognized that ginseng helped diabetes centuries ago. Sotaniemi et al[150] found 200 mg/day ginseng for eight weeks improved mood and physical activity, and lowered fasting blood glucose, glycosylated hemoglobin, and body weight compared to placebo. This dose is exceedingly moderate, and could be safely increased.
4. Onions and Garlic *(Allium cepa, Allium sativum).* Onions and garlic have been used in many cultures to treat diabetes, but are probably best utilized as adjuncts to other herbal and nutritional treatments. Onions and garlic both contain disulfide-bonded thiosulfinates and diallyldisulfides. Insulin has a similar disulfide bond, so *Allium* disulfide chemicals are

[f] Since gurmar appears to act primarily by stimulating insulin secretion, it may not be appropriate for chronic hyperinsulinemia.

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thought to compete with insulin for endogenous insulin-inactivating compounds. A very large dose of 10 gm/kg onion or garlic extract lowered fasting blood glucose and improved glucose tolerance by 7–18%.[135]

A review by Koch and Lawson[151] found lower doses of garlic are effective; however, most of the studies cited are older and uncontrolled. Newer studies indicate the sulfur-containing phytochemical s-allycysteine sulfoxide (alliin) may indeed be important for garlic to be effective. Garlic and onion lipid fractions (about 1-3% by weight) contain the majority of this phytochemical. In an open study, a single dose of 125 mg/kg onion oil lowered fasting glucose in six subjects from 75 to 59 mg/dl, while those receiving placebo went from 72 to 66.5 mg/dl. In this study, placebo also significantly reduced blood glucose, and the dosage translates to 12.5 g onion oil for a 100 kg human, so it may not represent a realistic clinical approach. In a double-blind study of 20 subjects, 800 mg/day garlic standardized for alliin (dose not specified) was given for four weeks. The 10 receiving garlic significantly lowered their fasting blood glucose from 90.6 to 77.8 mg/dl, while 10 receiving placebo went from 88.6 to 85.8 mg/dl, a nonsignificant change. In another study, spray dried garlic powder (which does not contain alliin) was given at 700 mg/day for a month, and had no effect.

Beyond Fiber

High fiber diets are uniformly recommended for diabetics.[14] Particularly important is soluble fiber, found mainly in fruits, vegetables, and some seeds. Insoluble fiber is more characteristic of brans and husks of whole grains, nuts, and seeds. Soluble fibers include pectins, gums, and mucilages, which act to increase the viscosity of food in the intestine, thus slowing or reducing the absorption of glucose. In this respect, any diet featuring large quantities of raw or lightly processed vegetables is beneficial. Our evolutionary diet was unprocessed and often rich in fresh vegetation and soluble fiber; however, today many shun vegetables rich in soluble fiber such as okra, turnips, and parsnips. Herbs and foods with high levels of pectin or mucilage have been used successfully for diabetes, and as discussed below, the soluble fiber is effective. However, some of these botanicals provide synergistic benefits beyond the physical effect of inhibiting glucose absorption.

1. Flax seed (*Linum usitatissimum*). Flax seed meal is one of the richest sources of soluble and insoluble fiber known. Cunnane et al[152] administered 50 g glucose along with plain water, or water containing mucilage extracted from flax seed to four nondiabetic subjects. The flaxseed mucilage dose decreased the area under the glucose tolerance curve by 27% compared to water. Six others were given 50 g white bread or bread with 25 wt% flax meal. The flaxseed bread decreased the area under the glucose tolerance curve by 28% compared to plain bread. Since the mucilage content of flaxseed meal is only a few percent, the effect is greater than can be accounted for by simple inhibition of glucose absorption. Flax seed is the richest food source of lignans[153,(footnote g)] and is also rich in protein, PUFA, and minerals,[154,155,(footnote h)] all of which may be beneficial.

2. Fenugreek (*Trigonella foenum-graecum*). Fenugreek is another Ayurvedic tradition proven effective. Whole fenugreek seeds are about 50% fiber, with 20% of that mucilage. In a double-blind study, 10 Type I diabetics were given meals with 100 g/day fenugreek powder (ground defatted,

[g] Thompson et al[153] report 52,675 mg/gm lignan excretion from ingesting whole flax seed; 67, 541 mg/gm from flax meal; the next closest source is legumes with 201-1287 mg/gm.

[h] Especially K, Mn, Cu, Zn, Ca. Flaxseed contains 5600-9200 mg/kg K on a dry weight basis, more than any other food source.[154]

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debitterized seeds) or regular meals. After 10 days, fasting glucose decreased by 30%, and glucose tolerance improved in the fenugreek group. Sugar excretion dropped an astonishing 54%, yet there was no increase in insulin levels.[156] Since fasting glucose was strongly affected, simple inhibition cannot be the only explanation. In addition to mucilage, fenugreek also contains protein, saponins, and the hypoglycemic phytochemicals coumarin, fenugreekine, nicotinic acid, phytic acid, scopoletin, and trigonelline.[40,131] In other double-blind studies, 15–25 g fenugreek powder were similarly effective for Type II diabetics.[157] In all studies, fenugreek was very effective at lowering LDL cholesterol and triglycerides.

3. Nopal (*Opuntia spp.*). Widely used throughout Latin America, nopal (prickly pear cactus), is rich in pectin. Nopal is a traditional food of Native Southwestern hunter-gatherers.[43] Frati et al[158] gave eight fasting diabetics 500 g nopal. Five tests were performed on each subject, four with different cooked or raw cactus preparations and one with water. After 180 minutes, fasting glucose was lowered 22-25% by nopal preparations, as compared to 6% by water. In a rabbit study, nopal improved tolerance of injected glucose by 33% (180 minute value for comparison) as compared to water.[136] In both these cases there was no glucose in the intestines. A purified extract of *Opuntia fuliginosa* given at 1 mg/kg/day for eight weeks along with insulin normalized blood glucose in diabetic rats. For the following seven weeks the *O. fuliginosa* extract was given alone, and glycemic control was maintained. *O. fuliginosa*, but not insulin, also normalized glycosylated hemoglobin levels; clearly, these results preclude a predominant role for the "fiber effect" alone.[159] The nopal researchers concur that although the cooked and raw cactus were effective, preparations from commercially dehydrated nopal are not effective. In addition, not all species of Opuntia are similarly effective.

4. Ivy gourd *(Coccinia indica)*. In a double-blind study of 32 diabetics, six tablets of ivy gourd leaves per day for six weeks decreased fasting glucose and improved glucose tolerance by 20%.[160] Although ivy gourd in rich in pectin, it also helps inhibit gluconeogenesis and stimulate glucose oxidation.

Other plants which may have the antidiabetic "soluble fiber plus" synergy are aloe vera, Indian cluster bean, and carrots, and there are doubtless more to be discovered and clinically tested. In summary, every effort should be made to encourage diabetic individuals to increase produce consumption; however, if compliance is a problem, similar benefits can be obtained with quantitatively lesser amounts of particular botanicals. There is good evidence that many botanicals have benefits for controlling diabetes that act on the cellular metabolic level, going far beyond the simple inhibition of glucose absorption.

Summary And Recommendations

Human nutritional needs are strongly dictated by Paleolithic hunter-gatherer needs and lifestyles. As far as *Homo sapiens* is concerned, agriculture is a new experience. "Genetic susceptibility" to NIDDM may be universal in *H. sapiens*, and the degree to which the disease progresses is potentially due to 1) the degree to which the diet strays from the evolutionary food types; 2) the degree to which the diet strays from the evolutionary micronutrient and triglyceride balance; 3) variable gene expression resulting from (1) and (2). Ethnic minority populations adopting Western dietary habits are particularly prone to NIDDM.

Nutritional intervention is required in order to prevent the initiation of insulin resistance and glucose intolerance which can progress to NIDDM. Maintaining a high lean/fat body mass ratio and regular exercise are of critical importance. Consuming foods more closely aligned with a hunter-gatherer diet can

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reduce obesity and provide glycemic control in many individuals. Both individuals and ethnic groups vary in their ability to metabolize grains, dairy products, and alcohol. Consuming dietary carbohydrates from fresh vegetable and fruit sources, which was the only option normally available to our ancestors, is recommended due to the synergistic benefits of fiber, phytochemicals, and a low density of carbohydrate per unit food weight. Those who do not choose to eat adequate produce can benefit from a number of herbal dietary supplements, which provide not only soluble fiber, but also phytochemicals which directly influence glucose metabolism.

Both the quantity and type of fat ingested greatly influence insulin sensitivity. Reducing total fat, SFA, n-6 PUFA, and increasing n-3 PUFA is generally recommended; however, there is evidence for variation in PUFA intake and metabolism throughout the population. Some ethnic groups with high NIDDM incidence may not convert PUFA to LC-PUFA as efficiently as other groups. A good rule of thumb is to supplement PUFA in a 1:1 n-6 to n-3 ratio, since Western diets are typically "front-loaded" with n-6 PUFA. A combination of LA, LNA (18-carbon PUFA) and LC-PUFA maximizes benefits while minimizing risks.

Chromium supplementation at 200-400 mcg/day might be preventive for NIDDM; however, dosages at or above 1000 mcg/day might be required to reverse or improve existing diabetic symptoms. Typical Western diets high in fat, grain products, and sugars not supplemented with Cr might not afford protection from NIDDM, regardless of the degree to which the foods are refined; however, development of glucose intolerance will be hastened when foods are highly refined.

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