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PERSPECTIVES

How Western Diet And Lifestyle Drive The Pandemic Of Obesity And Civilization Diseases

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Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Abstract: Westernized populations are plagued by a plethora of chronic non-infectious degenerative diseases, termed as "civilization diseases", like obesity, diabetes, cardiovascular diseases, cancer, autoimmune diseases, Alzheimer's disease and many more, diseases which are rare or virtually absent in hunter-gatherers and other non-westernized populations. There is a growing awareness that the cause of this amazing discrepancy lies in the profound changes in diet and lifestyle during recent human history. This paper shows that the transition from Paleolithic nutrition to Western diets, along with lack of corresponding genetic adaptations, cause significant distortions of the fine-tuned metabolism that has evolved over millions of years of human evolution in adaptation to Paleolithic diets. With the increasing spread of Western diet and lifestyle worldwide, overweight and civilization diseases are also rapidly increasing in developing countries. It is suggested that the diet-related key changes in the developmental process include an increased production of reactive oxygen species and oxidative stress, development of hyperinsulinemia and insulin resistance, low-grade inflammation and an abnormal activation of the sympathetic nervous system and the renin-angiotensin system, all of which play pivotal roles in the development of diseases of civilization. In addition, diet-related epigenetic changes and fetal programming play an important role. The suggested pathomechanism is also able to explain the well-known but not completely understood close relationship between obesity and the wide range of comorbidities, like type 2 diabetes mellitus, cardiovascular disease, etc., as diseases of the same etiopathology. Changing our lifestyle in accordance with our genetic makeup, including diet and physical activity, may help prevent or limit the development of these diseases.

Keywords: diabetes, obesity, metabolic syndrome, insulin hypersecretion, oxidative stress, paleolithic diet, pathogenesis

Introduction

Over the course of 6–8 generations, but especially in the last 2–3 generations, there has been an epidemic of obesity and non-infectious degenerative diseases known as "civilization diseases". While infectious agents were the major causes of disease at the beginning of the 20th century, infectious diseases were replaced by type 2 diabetes mellitus (T2DM) and diabetic complications, cardiovascular diseases (CVD) and cancer as major causes of death by the 21st century. At present, westernized populations are plagued by a plethora of chronic degenerative diseases, including obesity, T2DM, atherosclerosis, coronary heart disease, stroke, autoimmune diseases, essential hypertension, cancer, osteoporosis and other more, and the number of these diseases is also rapidly increasing in developing countries.[1–3]

In striking contrast, obesity and civilization diseases are rare or virtually absent in hunter-gatherer (HG) and other non-westernized populations. Also, low serum

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insulin levels and persistently excellent insulin sensitivity are characteristic of HG, but only as long as these people adhere to their traditional "paleolithic" diets.[2,4–7] Otherwise, transition to a "Western diet" (WD, as defined below) invariably leads to a dramatic increase in insulin resistance (IR) (defined here as an impaired ability of the hormone to suppress hepatic glucose output and to promote peripheral glucose disposal) and hyperinsulinemia as well as obesity, T2DM, hypertension, cancer and other more.[4,6,7] On the other hand, a return to a traditional paleolithic diet is associated with marked improvement in IR and fasting insulin levels[5,8,9] and glucose control and lipid profiles of T2DM.[8,9] The common counter-argument that Stone Agers usually do not live long enough to develop degenerative diseases is not accurate. A conspectus of data on HG societies suggests that modal age of adult death is about seven decades (adaptive life span of 68–78 years). In contrast to most Westerners, these people tend to be healthy up to old age. Causes of death are predominantly infectious diseases, while chronic degenerative disorders are rare.[10]

Numerous authors have argued that a mismatch between our ancient physiology and the WD and lifestyle play a key role in the development of many of these degenerative diseases.[2–4,7,11,12] Though, the question still remains: how do diet and lifestyle cause or contribute to the developmental process?

This paper shows that the significant changes in diet and lifestyle during recent human history cause severe metabolic distortions, which play a pivotal role in the development of degenerative diseases.

Important Differences Between Paleolithic And WDs

"Living organisms thrive best in the milieu and on the diet to which they were evolutionarily adapted; this is a fundamental axiom of biology".[11] This statement is based on the fact that the metabolism of each species has genetically adapted to a particular type of food over long periods of evolution. The specific diet guaranties health and survival.[11,13] Man is no exception in this regard. Like all species, today's humans are genetically adapted to the environment in which their ancestors survived and in which their genetic makeup was selected.[4,13] The evolutionary adaptation process has produced a specific, well-adjusted metabolism in which numerous metabolic factors are intertwined and in balance with each other.

A comparison of 229 HG diets from around the world found that these diets are higher in protein (19–35% of energy) and low in carbohydrate (22–40% of energy) by normal western standards, whereas the fat intake would be comparable or higher (28–58% of energy) than values currently consumed in modern, industrialized societies.[14] HG diets consisted mainly of game, fish and uncultivated plant-based foods such as roots, tubers, wild herbs, berries, nuts, vegetables, fruits and some honey, while cereals, refined sugars and dairy products were not part of it.[4,7,12,14,15] More importantly, all carbohydrate foods (other than wild honey) that were consumed during the Paleolithic were low-glycemic and low-insulinemic in effect.[4,12,15–17] Since the effect of protein and fat on insulin production is small too,[18] postprandial glucose and insulin levels were low during most part of human evolution.

With the agricultural revolution about 10,000 years ago and especially since the industrial revolution 250 years ago, human nutrition has changed significantly. At present, carbohydrates play an enormously important role in the human diet. WDs consist of large amounts of high-glycemic/high-insulinemic carbohydrate foodstuff like refined cereals (currently, 85% of the cereals consumed in the US diet are highly processed refined grains[4]), corn, potatoes and sugars (in particular sucrose and fructose), dairy products (which also produce high postprandial insulin levels, despite a low GI, not significantly different from the Insulinemic Index of the reference bread[18,19]), as well as high amounts of fat and substantial amounts of protein. Glucose, which is abundantly derived from carbohydrate sources, especially from starchy foods and sugars, is currently the most important source of energy for the human body and accounts for about 40–75% of the energy intake.

Furthermore, due to agribusiness and modern agriculture, WDs contain excessive amounts of omega-6 polyunsaturated fatty acids (PUFAs) and only small amounts of omega-3 PUFAs, resulting in an unhealthy omega-6/omega-3 ratio of 20: 1 compared to a balanced ratio during the Paleolithic period. The consumption of the omega-6 PUFAs has dramatically increased in the western world primarily in the form of vegetable oils. A diet rich in omega-6 fatty acids is proinflammatory and prothrombotic, and has been implicated in the development of various degenerative diseases, including T2DM, CVD, cancer, obesity inflammatory bowel disease, major depression, Alzheimer's disease and other more.[20–22]

However, while a higher intake of omega-3 fatty acids has been associated with reduced risks of cardiovascular disease and cancer in several observational studies, a

recently published, randomized placebo-controlled study found that supplementation with n-3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo.[23]

Lack Of Genetic Adaptation

While human nutrition has changed significantly over the last 10,000 years, and especially over the last 250 years, the human genome has remained largely unchanged. Changes in diet and lifestyle occurred too fast for the human genome to adapt to, therefore, humans are still biologically adapted to the environment of their preagricultural ancestors.[13] It further has to be considered that an evolutionary adaptation process needs selection pressure (external agents which affect an organism's ability to survive in a given environment) as a driving force. However, degenerative diseases such as atherosclerosis, hypertension, cancer, T2DM, etc. normally affect the post-reproductive years. Even a high mortality rate due to these diseases after the reproduction phase will produce little or no selective pressure.

The significant changes in diet and lifestyle during recent human history cause severe metabolic distortions, including (but not limited to) a diet-related increased production of reactive oxygen species (ROS) and oxidative stress (OS), hyperinsulinemia and IR, low-grade inflammation and an abnormal activation of metabolic systems such as the sympathetic nervous system (SNS) and the renin-angiotensin-system (RAS), all of which play pivotal roles in the development of civilization diseases (Figure 1).

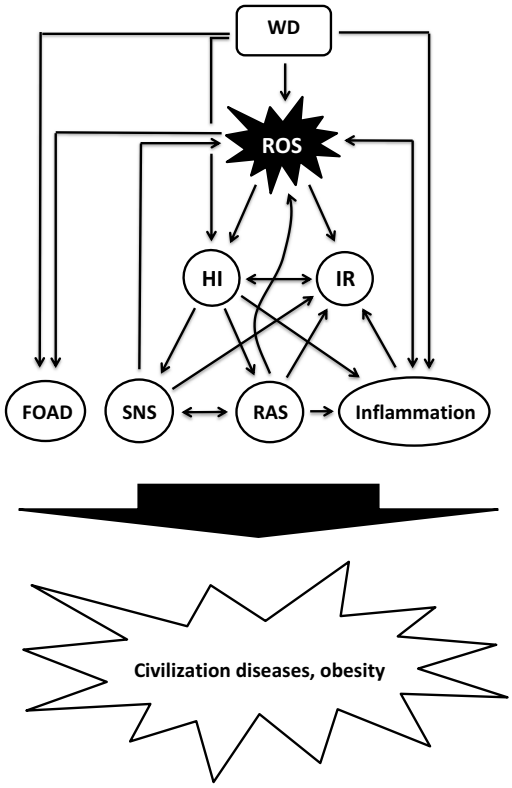

Figure 1 Proposed model of diet-induced development of obesity and civilization diseases.

Abbreviations: FOAD, fetal origin of adult disease; HI, hyperinsulinemia; IR, insulin resistance; RAS, renin-angiotensin system; ROS, reactive oxygen species; SNS, sympathetic nervous system; WD, Western diet.

Reactive Oxygen Species (ROS) – Friend And Foe

A growing body of evidence suggests that ROS play a dual role both as signaling molecules and as a damaging agent. On the one hand, ROS are an inevitable byproduct of the mitochondrial respiratory chain activity. Some of the electrons transferred along the electron transport chain (ETC) escape, and the sequential reduction of oxygen through the addition of electrons leads to the formation of a number of ROS, including superoxide, hydrogen peroxide (H2O2), hydroxyl radical, hydroxyl ion, and nitric oxide. On the other hand, ROS are deliberately produced in low concentrations in the form of the chemically less reactive H2O2 and serve as important signal molecules.[24] Under physiological conditions, there is a balance between ROS generation and clearance, since eukaryotic cells have several antioxidative defense mechanisms, but these defenses are not perfect. Excessive formation of reactive species that is not counterbalanced by antioxidant defense mechanisms leads to OS which causes damage to lipids, proteins and DNA. In addition, increased ROS production and OS can interfere with intracellular signal transduction processes, which has been implicated in the development of IR, inflammation[25,26] and various civilization diseases like cancer, CVD including atherosclerosis, cardiomyopathy, hypertension and heart failure, and other more.[26–28]

Oxidative Phosphorylation (OXPHOS) - A Demand-Driven Process

The primary role of mitochondria is the generation of energy and the regulation of cell metabolism. Mitochondria are responsible for the bulk of cellular adenosine triphosphate (ATP) production through OXPHOS. The macronutrients carbohydrates, fat and proteins, the primary catabolic substrates that provide the most energy to humans, are broken down into glucose, fatty acids and amino acids. Glucose and

free fatty acids (FFA) serve as major fuels that can be oxidized for ATP production in mitochondria, while amino acids serve to form new proteins or as an energy source. Glucose and FFA are further degraded to acetyl-coenzyme A (acetyl-CoA). From acetyl-CoA, the reducing agents NADH and FADH2 are formed in the tricarboxylic acid cycle, which release electrons to the mitochondrial ETC. The sequential transport of electrons pumps protons through the inner mitochondrial membrane and creates an electrochemical gradient. The final acceptor of electrons in the ETC is molecular oxygen, yielding water and ATP.[29] Basically, OXPHOS is a demand-driven process where energy supply is matched to ATP demand, regulated by adenosine diphosphate availability; therefore, a diet-related increase in electron delivery does not necessitate a proportional increase in ATP production. When electron supply exceeds demand for ATP, mitochondrial membrane potential rises, resulting in the production of increasing amounts of ROS.[30–32] Therefore, nutrient excess can lead to increased production of ROS and OS.[30,33]

WDs, Western Lifestyle And Oxidative Stress

At present, human physiology is characterized by overeating, with frequent snacking and consumption of sucrose-containing soft drinks. "X-large" is the motto for meals and beverages. Specifically sugar is easily consumed in large quantities, not only in beverages, but also as sweets and as an additive in bakeries and ready meals. As a result, a significant part of the day is spent in the postprandial state, and the postprandial state is characterized by a persistent abundance of substrate in the circulation.[34] Insulin levels are elevated for much of the day. Since foods with a high insulin response produce appetite and are less satiating,[35–37] high-insulinemic WDs directly promote increased food intake and overeating. In addition, the energy density of food has a major impact on the regulation of food intake and body weight. Foods with high energy density content, like WDs, are more palatable, but less satiating and lead to a high energy intake.[38] Also, calories from fluids are less satiating than those from solid foods and often lead to overconsumption.[39]

The glycemic index and the glycemic load (GL, the multiplicative product of carbohydrate amount and GI)[16] of a meal are major determinants of post-prandial glucose excursion. WDs therefore often are associated with exaggerated supraphysiological postprandial peaks in blood sugar and lipids.[32] Because OXPHOS is a demand-driven process, the bolus of energetic substrate in a high-calorie, low-energy situation can overwhelm the metabolic capabilities of mitochondria, resulting in an excess of the reduced form of nicotinamide adenine dinucleotide production, depolarization of mitochondrial membrane potential and OS.[30–33] The level of OS is directly related to the increase in glucose and triglyceride levels after a meal.[32]

In addition, WDs and nutrient excess can cause mitochondrial dysfunction and increased ROS production through adverse effects on the mitochondrial life cycle[40] and through mitochondrial overload and metabolic inflexibility.[30]

Consistent with the above, diets with a high GL,[41] high-sucrose diets[42] and WDs[33,43,44] produce high levels of ROS. Postprandial glucose excursions correlate directly with the ensuing increase in free radicals.[32,45] In contrast, Paleolithic and Mediterranean diets are associated with low OS.[46]

Diet-Related Development Of Hyperinsulinemia And IR

IR is of paramount importance for the pathogenesis of civilization diseases, but the mechanism is still not clearly identified. Visceral adiposity is traditionally considered to be the cause of IR and compensatory hyperinsulinemia, based on the assumption that increased adipose tissue mass causes increased release of FFA into the portal vein system, which in turn promotes IR in target tissues, but the picture is not as clear as it seems, and this assumption has been challenged for several reasons.[30,47–50] Further, not all obese individuals are insulin resistant, while IR has been shown to exist in a significant proportion of the normal weight population.[51] Alternatively, an excessive ß-cell secretory response has been suggested as a major cause of both, obesity and IR.[48–50,52–54] Indeed, hyperinsulinemia has been found to precede the development of IR and obesity.[49,54–58] Also, early hyperinsulinemia was the strongest predictor of T2DM in a 24 year study.[59] Persistently elevated levels of insulin, regardless of their source, were shown to produce IR[60–63] and to impair insulin-stimulated glucose uptake and its cellular signaling in a dose-dependent manner.[63] An insulin-related overactivation of the SNS[64] and RAS[65,66] may also play an important role (see below).

A growing body of evidence suggests that increased ROS levels and OS play a major role in the development of hyperinsulinemia,[48,67,68] IR[28,40,63,69–73] and obesity.[74]

ROS are essential for the regulation and coordination of insulin production: nutrient-mediated ROS production

(in the form of H2O2) is used in β-cells to couple nutrient (glucose, FFAs, amino acids) oxidation to insulin secretion.[48,67] Pi et al[67] showed that ROS (added as H2O2 or generated internally through addition of diethyl maleate) stimulate insulin secretion in a dose-dependent manner. While increased ROS production stimulates basal insulin secretion,[67,68] scavenging ROS prevents both basal and stimulated insulin secretion.[48,67,68]

Elevated ROS levels from various sources, including nutrient/energy surplus,[25] FFA,[69] hyperinsulinemia,[62] RAS,[25,70] SNS,[71,72,75] inflammation,[72] metabolic inflexibility[30] and mitochondrial fission[40] were shown to be important triggers for IR. Otherwise, induction of insulin resistance in cultured cells is blocked when ROS are scavenged.[73]

WDs can play a causative role in the development of hyperinsulinemia and IR (prior to weight gain), as they produce high levels of both insulin and OS. On the one hand, WDs,[33,43,44,76] high-sucrose diets,[42,77] diets with a high GL[41] and high-fructose diets[78] produce high levels of ROS and OS which may cause IR and insulin hypersecretion. Increased ROS production and OS were shown to precede the onset of IR and obesity in mice fed a high-fat diet.[79] Also, chronic exposure of β-cells to excess nutrients (in the form of glucose and oleate) has been shown to promote insulin hypersecretion, probably due to increased ROS production.[68,69]

On the other hand, WDs induce a high postprandial insulin response. Along with a western dietary pattern of frequent snacking and frequent consumption of sucrose-containing soft drinks, the associated high insulin requirement places strain on β-cells. Because beta cells are, from an evolutionary point of view, genetically poorly adapted to high insulin requirements, high-insulinemic diets may cause hypertrophy and dysfunction, finally resulting in hyper-responsiveness and hypersecretion in response to normal meals.[49,50,52,57,80–82] Indeed, hyperinsulinemia was shown to be associated with pancreatic islet cell hyperplasia and enhanced secretory capacity.[49,57,80–84] In line with this, an increased postprandial insulin response, probably due to ß-cell dysfunction and dysregulation, was the earliest metabolic change in the development of adiposity in adolescents in a study by Le Stunff,[57] followed by the parallel, time-dependent development of IR and fasting hyperinsulinemia. A study of insulin dynamics among obese schoolchildren suggested that hypersecretion precedes development of insulin resistance by several years.[85] Further, rat puppies fed a high carbohydrate-rich formula developed hyperinsulinemia, hyperphagia and concomitant body weight gain. Moreover, the metabolic alterations persisted in adult rats and were even passed on to the next generation.[86] Prolonged feeding of Wistar rats with a diet high in glycemic index starch and fat, similar to WDs, resulted in insulin hypersecretion and weight gain.[87] Wistar rats developed hyperinsulinemia on a high-sucrose diet.[88] Also, Fisher rats fed ad libitum with a high-fat, refined sugar diet developed hyperinsulinemia and IR before gaining weight.[89,90] Intriguingly, IR developed, regardless of whether dietary fat was high (39.5%) or low (9%), pointing to sucrose as the determining factor.[90] Fructose, for example in the form of fructose corn syrup or as a constituent of sucrose (consisting equally of glucose and fructose), seems to play a particularly important role in the pathogenic process, especially given the enormous amounts consumed (as sweetener for soft drinks and additives for ready meals). The consumption of fructose corn syrup increased >1000% between 1970 and 1990.[91] Feeding studies have shown that diets rich in fructose cause hyperinsulinemia,[92] IR,[78,93] and OS.[78] Further, in a study on 8-year old schoolboys, high intake of (high-insulinemic) milk caused hyperinsulinemia, IR and weight gain.[18]

Finally, it is well established that IR also has a genetic component. Young healthy offspring of hypertensive parents and parents with T2DM are insulin resistant and have higher plasma insulin levels compared with matched healthy individuals with negative family history.[94,95] WDs could be involved in this genetic inheritance: as mentioned above, rat puppies fed a high carbohydrate-rich formula developed IR, which was passed on to the next generation.[86]

Overactivation Of The SNS

The SNS is involved in the regulation of the microenvironment of virtually every major organ system of the body by releasing two catecholamine neuroeffector molecules, norepinephrine (NE) and epinephrine which act as both neurotransmitters and circulating hormones. NE is released primarily from the sympathetic nerves, while epinephrine is mainly secreted from the adrenal medulla. Adrenergic receptors are expressed on virtually every cell type in the body. A body of evidence supports the view that increased activation of the SNS is a hallmark of obesity and its associated metabolic disorders and may play an important role in a variety of other degenerative diseases.[96]

There is a close relationship between insulin and the SNS: insulin activates the SNS in a dose-dependent manner in normal individuals, as indicated by elevated NE plasma levels (due to sympathetic nerve endings spillover) and micro-neurographic studies.[64] SNS activity is also influenced by food intake: among dietary substrates,

ingestion of high-insulinemic carbohydrates, like starch and sugars, substantially enhances SNS activity, characterized by a significant increase in plasma NE levels,[97] while protein or fat ingestion exert minimal effects on NE levels only.[98] Diet composition therefore plays a major role in determining the level of SNS activity. In feeding studies, high carbohydrate/protein diets were associated with a significant increase in NE levels, while high fat/protein diets did not alter SNS activity.[99,100]

Furthermore, increased activation of the SNS, whether caused by lower body negative pressure or NE infusions promotes IR,[71,101] probably due to OS,[72,75] while ganglionic blockade in turn improved insulin-sensitivity.[102] While sympathetic overactivation contributes to IR, the compensatory increase in insulin levels may contribute to greater sympathetic activation, consistent with the existence of a negative feedback loop.[102] As with hyperinsulinemia[56,57] and OS,[79] elevated NE levels precede the development of IR.[103]

Overactivation Of The RAS

The RAS plays an important role in normal physiology as well as in pathologic conditions. The classical view of the RAS is presented as a hormonal circulating system, with angiotensin II (ANG II) as the major effector peptide. In addition to the classic hormonal circulating system, a local RAS exists in various organs and tissues, leading to production of ANG II, with autocrine and paracrine effects.[104,105] Several metabolic factors can activate the RAS, including insulin[65,66] and the SNS.[63,106,107] Acute hyperinsulinemia increases plasma renin activity and plasma level of ANG II.[65,66] The SNS can interact with the RAS in the form of a positive feedback loop: NE activates ANG II production through stimulation of renin secretion, whereas circulating ANG II interacts with the SNS at various sites and amplifies the response to sympathetic stimulation by presynaptic facilitatory modulation of NE release.[106,107] Clinical and pharmacological studies have shown that ANG II is a critical promoter of IR,[70,108] subclinical inflammation and OS.[109,110]

Overactivation of the SNS and the RAS plays an important role in a variety of degenerative diseases, including CVD, T2DM, cancer, and many more.[103,109–113]

Widespread Activation Of The Immune System And Low-Grade Inflammation

A fundamental feature of the immune system is to protect the host from pathogens. Inflammation is a central component of innate (non-specific) immunity. The inflammatory response serves to initiate the elimination of toxic agents and the repair of damaged tissues. After activation, innate immune system cells secrete proinflammatory cytokines that induce production of free radicals (ROS and reactive nitrogen species). The inflammatory response continues until the pathogens are eliminated and the tissue repair process is complete.[114]

An increasing body of evidence shows that chronic inflammation causes and advances many common diseases, including obesity, T2DM, CVD, inflammatory bowel disease, osteoarthritis, autoimmune diseases, to name a few.[115]

On the one hand, chronic inflammation causes OS, on the other hand, OS plays a crucial role in the development and perpetuation of inflammation, indicating that inflammation and OS are pathophysiological events that are closely related.[116] In addition to OS, hyperinsulinemia,[49,117,118] ANG II[109] and activation of the SNS[119] are also causally related to the development of chronic subclinical inflammation, linking insulin-resistant states like obesity and T2DM to inflammation. WDs were shown to reprogram the innate immune system and induce low-grade inflammation.[21,120] In contrast, a low-GL diet reduces inflammation and tends to increase a beneficial adipokine (adiponectin) in overweight and obese but otherwise healthy adult men and women.[121]

Obesity And Civilization Diseases As A Manifestation Of (Diet-Related) Metabolic Changes (Figure 1)

The next section provides representative examples to explain the important role played by the metabolic alterations described above in the development of obesity and civilization diseases.

WDs And Obesity

Since 1980, the prevalence of obesity has doubled in more than 70 countries and continues to rise at an alarming rate in both developed and developing countries. While the prevalence of overweight and obesity among children and adolescents changed very little between the 1960s and early 1980s, dramatic increases were observed during the 1980s and 1990s. The obesity epidemic was first noted in the U.S, but during the last few decades, this phenomenon has spread to all parts of the world. Obesity is now considered as a pandemic condition, with serious health

implications. Despite intensive research, the causes of the obesity epidemic remain incompletely understood.[122–125] It is widely held that obesity results from a chronic surplus of energy intake compared to energy expenditure, which leads to storage of excessive amounts of triglycerides in adipose tissue. Multiple factors are thought to interact to produce a state of positive energy balance, including genetic and epigenetic factors, diet, lifestyle and lack of physical activity.[122–125] Although genes may contribute to a person's susceptibility to weight gain,[126] genetic changes are unlikely to explain the rapid spread of obesity around the globe during the last decades.[127]

While high calorie intake combined with low physical activity certainly plays an important role in the development of obesity, diet-related metabolic alterations may be even more important. Mixed diets such as WDs (which provide high levels of glucose and FFA that compete for mitochondrial oxidation) are characterized by daily oscillations between glucose and FFA oxidation, which are coordinated by insulin and glucagon. During the fed state, a high insulin/glucagon ratio promotes lipid storage and suppression of gluconeogenesis, while in the fasted state a high glucagon/insulin ratio stimulates lipolysis and hepatic glucose production to provide glucose supply to glucose-dependent tissues. Hence, during the fed state, glucose serves as main fuel and fat is stored, while during the fasted state, fatty acids serve as main fuel and glucose is preserved for glucose-dependent tissues.[30,35,128] Mobilization and oxidization of FFA in the fasted state (as well as during enhanced physical activity) are only possible as long as insulin levels are not elevated. As mentioned earlier, due to the westernization of diet and lifestyle, insulin levels are increased much of the day.[34] High postprandial insulin levels drive fat storage and prevent lipolysis while maintaining FFA re-esterification.[49,53,54,129] As a result, part of the (daily) stored FA can remain stored and contribute to a gradual increase in fat mass.[49,53,54,125,129] However, the most important metabolic alterations may be the development of insulin hypersecretion and hyperinsulinemia, which significantly accelerates weight gain.[49,50,54–57,125,130] Several studies in humans[18,57,130,131] and animals[56,58,89,90] support a causal role of hyperinsulinemia in the development of obesity. High rates of weight gain occurred in individuals who presented with a high acute insulin response to glucose and this effect was particularly manifested in insulin-sensitive individuals.[130] The Da Qing Children Cohort Study showed that fasting insulin at the age of 5 years (even after adjustment for age, sex, birth weight, TV-viewing time and weight at baseline) predicted weight gain from age 5 to 10 years.[131] Odelye et al[55] demonstrated that fasting plasma insulin concentration correlates with the rate of weight gain. Also, a study of insulin dynamics among obese schoolchildren suggested that insulin hypersecretion precedes development of insulin resistance by several years.[85] A study performed with knockout mice confirmed that hyperinsulinemia alters lipid metabolism and promotes obesity.[49] Otherwise, inhibition of hyperinsulinemia with diazoxide or octreotide causes weight loss and decreases insulin levels without impairing glucose tolerance in obese humans.[132] Development of IR prevents unlimited insulin-induced weight gain.[133] As previously described, high-insulinemic diets, including WD, may play an important role in the development of insulin hypersecretion and (fasting) hyperinsulinemia.[18,85–90] Also, several studies support a causal role of high-insulinemic diets in the development of obesity.[89,134,135] In addition, high insulin levels lead to increased appetite, hyperphagia and carbohydrate craving.[36,37,139] Several studies have also found that foods with high insulin responses are less satiating.[35] Finally, high dietary intake of omega-6 PUFAs also has been implicated in the development of obesity.[21]

Genetic factors may account for differences in sensitivity and reactivity of β-cells to high-insulinemic foods, and thus for exaggerated insulin secretion (hypersecretion). This is supported by a study which found that variants in the insulin promoter gene were associated with insulin hypersecretion and strongly predicted weight gain.[136]

Furthermore, adipose tissue is not only the primary storage site for excess energy, but also a metabolically active organ that excretes a variety of biologically active molecules, which are believed to play a role in the development of a variety of metabolic alterations, such as OS, insulin resistance, low-grade inflammations, mitochondrial dysfunction, β-cell dysfunction, and other more, which may contribute to the development of civilization diseases.[137,138]

In summary, diet composition and lifestyle play an important role in the development of obesity. WDs cause a high postprandial insulin production and can produce insulin hypersecretion and hyperinsulinemia, which promote fat storage, prevent lipolysis and cause increased appetite, hyperphagia and weight gain.[35–37,139] On the other hand, feeding studies that included only non-energy-restricted diets confirmed that caloric intake decreases spontaneously and weight loss is induced when carbohydrate intake is restricted.[35,139,140] In addition, several human and animal intervention studies showed that

Mediterranean or Paleolithic diets have highly beneficial effects on risk factors for diseases of civilization.[2,141–143]

Diabetes Mellitus

Global rates of diabetes mellitus have reached epidemic proportions and are associated with an ever-increasing health and socioeconomic burden. T2DM is a progressive disease due to IR and advancing β-cell dysfunction. OS is critically involved in the impairment of beta cell function due to the low antioxidant capacity of beta cells and has also been implicated in the progression of long-term T2DM complications, including microvascular and macrovascular dysfunction.[144] ANG II, independently of its vasoconstrictor action, causes OS, β-cell inflammation and dysfunction through enhanced activation of cellular NADPH oxidase via ANG II receptors.[112] The RAS is also considered to be involved in most of the pathological processes that result in diabetic nephropathy.[145] SNS overactivity almost doubled the risk of T2DM over an eight-year follow-up period in the Atherosclerosis Risk in Communities Study with more than 8,000 middle-aged non-diabetic adults at baseline.[146]

Cardiovascular Diseases

Endothelial dysfunction is a key factor in the development of CVD. A dysfunctional endothelium promotes vascular inflammation, infiltration and activation of inflammatory cells, chemokine and cytokine secretion, vasoconstriction, lipoprotein oxidation, platelet aggregation, white blood cell adhesion and proliferation, and apoptosis of endothelial and vascular smooth muscle cells, key factors in atherogenesis and hypertension.[147] OS,[148] overactivity of the RAS,[149] and IR and hyperinsulinemia[150,151] are causally related to endothelial dysfunction. Even modest hyperinsulinemia, comparable to fasting hyperinsulinemia of insulin-resistant conditions, can cause severe endothelial dysfunction in large conduit arteries.[150]

Further, subclinical inflammation is involved in all stages of the atherosclerotic process, from the initiation of fatty streaks to the development of plaque rupture and thrombus formation.[111,152] As mentioned before, hyperinsulinemia,[117,118] the SNS[119] and the RAS[109] are causally related to the development of subclinical inflammation.

The RAS,[109] the SNS,[153] insulin-related endothelin-1 production[154] and OS[28] promote proliferation, migration, senescence, apoptosis, autophagy of vascular smooth muscle cell and vascular remodeling of resistance vessels of the systemic circulation and of renal vessels, as well as peripheral and renal vasoconstriction and peripheral vascular resistance, increase heart rate, stroke volume, renin secretion and tubular sodium reabsorption, and thereby contribute to the development of hypertension and atherosclerosis.[111,149,155,156]

Activation of the RAS stimulates accumulation of low-density lipoproteins, particularly the oxidatively modified form, in blood vessels which plays an important role in atherosclerotic plaque formation, progression and destabilization.[157] According to the "oxidized linoleic acid theory of coronary heart disease", dietary linoleic acid, especially when consumed from refined omega-6 vegetable oils, gets incorporated into all blood lipoproteins (such as LDL, VLDL and HDL), increasing the susceptibility of all lipoproteins to oxidize and hence increases cardiovascular risk.[22] Further, plasma insulin concentrations are inversely related to HDL-cholesterol levels and positively associated with triglyceride levels, metabolic alterations strongly associated with atherosclerosis.[158]

Cancer

While the somatic mutation theory has been the prevalent theory in cancer research for the last 50 years, a body of evidence has accumulated showing that cancer is not only a genetic disease of uncontrolled cell proliferation, but also a metabolic disease.[128,159] OS,[27,44,116,160] hyperinsulinemia and IR,[161] the SNS,[113] the RAS[162] and inflammation[163] have been implicated as important causal factors for cancer development.

Epidemiological studies suggest that obesity and T2DM are positively correlated with both the risk of cancer. Among several factors that play a role, the most important link between obesity, T2DM, and cancer appears to be related to insulin resistance, hyperinsulinemia and increased levels of insulin-like growth factor (IGF). Hyperinsulinemia may affect cancer risk not only through direct mitogenic effects of insulin but also indirectly via increased production of IGF1. Hyperinsulinemia and augmented insulin and IGF1 signaling can enhance tumor development and growth.[164]

More……

Hyperinsulinemia, overactivation of the RAS and the SNS, inflammation and OS have been implicated in the development of Alzheimer disease[72,165–167] and benign prostatic hyperplasia and hypertension.[155] Hyperinsulinemia, overactivation of the SNS, inflammation and OS have been implicated

in the development and polycystic ovary syndrome.[160,168,169] Inflammation and OS contribute to the pathophysiology of a number of debilitating diseases, including nonalcoholic fatty liver, osteoarthritis, and autoimmune diseases, such as lupus and rheumatoid arthritis, Hashimoto thyroiditis, allergies, neurodegenerative disorders such as Parkinson's disease, multiple sclerosis and Major Depressive Disorder, Graves' disease, type 1 DM, psoriasis, asthma, inflammatory bowel disease, Crohn's disease.[115,118,170] Elevated NE tone has been suggested to be an etiological factor in open-angle glaucoma, osteoarthritis and rheumatoid arthritis, asthma, epilepsy, Parkinson disease.[167] The RAS has been implicated in the development of neurodegenerative diseases, such as multiple sclerosis, Parkinson, Alzheimer and Huntington disease.[171] In addition to its role in atherogenesis and hypertension, the RAS plays a critical role in the pathogenesis of many other types of CVDs including cardiomyopathy, valvular heart disease, aneurysms, infarction, stroke and renal disease.[109,172] Hyperinsulinemia and low-grade inflammation have been implicated in the development of osteoarthritis.[117]

This listing could continue, but that would go beyond the scope of this publication.

There are certainly more metabolic alterations involved in the development of civilization diseases that are not mentioned in this article. On the one hand, however, it is assumed that the changes described are most important because they affect powerful metabolic systems such as the SNS, the RAS and the immune system, on the other hand, it is likely that (at least many) alterations that have not been addressed are likewise part of the disrupted metabolic balance described above.

Important Life-Style Factors

In addition to the dietary patterns described above, a variety of life-style factors have been implicated in disease development, including smoking, overuse of alcohol, drug abuse, lack of physical activity and inadequate relief of chronic stress.[2,23,173–180]

Cigarette smoking can cause or contribute to the development of a range of potentially fatal and disabling diseases and conditions including several types of cancer, CVD, chronic obstructive pulmonary disease. Intriguingly, smoking causes OS,[173] IR,[174] activation of SNS[175] and the RAS,[176] and low-grade inflammation,[177] all of which have been implicated in the development of civilization diseases, as pointed out above.

Alcohol consumption, especially heavy drinking, is an important risk factor for many health problems and therefore contributes significantly to the global burden of disease. These include not only well-known outcomes of drinking such as liver cirrhosis or traffic accidents, but also categories of illnesses like infectious diseases, cancer, diabetes, neuropsychiatric disorders (including alcohol use disorders) and CVD. Most of the alcohol-related harm is caused by the regular consumption of alcohol. According to a study by the Centre for Addiction and Mental Health, about 40% of the world's adult population consumes alcohol, and the average consumption per drinker is 17.1 litres per year.[178,179]

Finally, a sedentary lifestyle and lack of physical activity of today's people has also been implicated in the development of civilization diseases.[180]

Microbiome

The human gut microbiota plays an important role in the health of the human host. An increasing body of evidence suggests that gut microbiota is adversely affected by a WD, which promotes inflammation resulting from both structural and behavioral changes in the resident microbiome, and that these changes are associated with obesity and metabolic diseases, including cancer, T2DM, asthma, psychiatric diseases and other more.[181] Otherwise, a Mediterranean diet rich in plant foods favorably influenced the microbiome-related metabolome profiles in persons who previously consumed a WD.[182]

Further, increasing evidence supports an important role of genetic and epigenetic mechanisms in disease development. Epigenetics deals with changes in DNA and histone proteins that alter tissue and cell type-specific gene expression patterns, thereby causing certain diseases, particularly some cancers. Prenatal exposure to various environmental factors (maternal stress, smoking, viral infections, drugs and toxins, etc.) may affect the fetal epigenome. In particular, maternal nutrition has a profound effect on the epigenome and can determine gene expression patterns and health throughout the life course[183,184]

The Fetal Origins Of Adult Disease (FOAD) Hypothesis

It is meanwhile well established that prenatal development is a critical period in the etiology of human diseases: the fetal origins of adult disease hypothesis implies that adverse influences during early development, in especially maternal nutritional imbalance and metabolic disturbances during pregnancy, lead to developmental adaptations in the fetus that permanently alter the structure, physiology, and

metabolism of the fetus ("fetal programming") and make individuals susceptible to the development of obesity and related diseases, such as T2DM, hypertension, CVD and other, from childhood to adulthood.[184–187]

Proper nutrition is a key factor for the correct somatic growth and development of the fetus. The availability of nutrients to the fetus depends on placental supply and maternal nutrition. Maternal nutrition, food supply and metabolism during pregnancy and lactation have therefore marked implications on child development and long-term health.[187,188]

Both in humans and animals models, maternal malnutrition (protein and/or calorie restriction) as well as overnutrition (especially with diets rich in fat, refined grains and sucrose, typical of WDs) can lead to an adverse metabolic profile and a tendency for IR, metabolic syndrome, T2DM, obesity, and CVD during adulthood.[186–190] Increasing evidence suggests that maternal hyperglycemia is also a risk factor for fetal programming and can down-regulate both fetal glucose tolerance and insulin sensitivity.[185,189,191]

Maternal obesity, excessive weight gain during pregnancy and gestational diabetes can also have significant adverse effects on fetal development, characterized by a tendency to obesity, insulin resistance, diabetes, hypertension and other more in later life.[186,189,192,193] In an animal model of maternal obesity, adverse metabolic effects in the offspring were compounded by a high-fat diet during pregnancy and lactation.[192]

Increasing evidence suggests that OS and epigenetic mechanisms are the link between adverse intrauterine environment and disruption of the normal pattern of fetal development. During pregnancy, ROS serve as signaling molecules to allow for the normal progression of embryonic and fetal development. An excess production in ROS during the intrauterine period leads to altered placental function and plays a central role in altered fetal programming.[186,194–197]

Obesity itself is characterized by chronic low grade inflammation with permanently increased OS. Maternal obesity is therefore associated with metabolic alterations and dysregulation of redox balance in the mother-placenta-fetus unit.[198] In addition, both maternal malnutrition and overeating are associated with OS and DNA methylation of selected gene promoter regions.[188,193,195–198] Diet composition plays an important role in this regard: WDs,[33,43,44,76] high-sucrose diets,[42,77] diets with a high GL[41] and high-fructose diets[78] produce high levels of ROS and OS. In contrast, Paleolithic and Mediterranean diets are associated with low OS.[46]

In search of the "perfect maternal diet", cohort studies indicate that dietary patterns which are mainly based on vegetables, fruits, whole grains, fish, chicken and lean meat have a positive effect on the formation of a normal placenta and the developing fetus and are associated with a reduced risk of pregnancy complications.[187,189,199]

Summary And Conclusions

- Over the course of 6–8 generations, but especially in the last 2–3 generations, there has been a pandemic of obesity and non-infectious degenerative diseases known as civilization diseases.
- Among a variety of factors that may be involved in this development, Western diet and lifestyle, as well as epigenetic changes and fetal programming, are believed to play key roles.
- The evidence presented shows that Western diets significantly distort the fine-tuned metabolism that has evolved over a very long period of human evolution in adaptation to Paleolithic nutrition, including an increased production of ROS, insulin hypersecretion and IR, low-grade inflammation and an abnormal activation of SNS and RAS (displayed in Figure 1), which may cause or contribute to the development of civilization diseases.
- The suggested pathomechanism is also well-suited to explain the well-known but not completely understood close relationship between obesity and the wide range of comorbidities like T2DM, cardiovascular disease, cancer, etc., as diseases of the same etiopathology.
- With the increasing spread of Western diet and lifestyle worldwide, overweight and lifestyle diseases are also rapidly increasing in developing countries.
- As rates of obesity increase worldwide, a significant percentage of embryos and fetuses will be exposed to an overweight or obese in utero environment and likely to maternal overnutrition during key periods of perinatal development, making fetuses vulnerable to obesity and degenerative diseases later in life - a self-reinforcing process that further fuels the pandemic.
- Changing our lifestyle in accordance with our genetic constitution, including diet and physical activity, can help prevent or limit the development of these diseases. This view is underpinned by several human and animal intervention studies which show that diets composed of Mediterranean/Paleolithic foods such as meat, fish, eggs, fresh fruits and vegetables, roots, tubers, nuts and seeds have highly beneficial effects on risk factors for diseases of civilization.[2,141–143,181]
- Probably more important than the foods contained in these diets are foods that are not included, especially

high-glycemic carbohydrate foods, like refined grains, sugar, corn, refined fructose, and foods that are high in omega-6 PUFAs. Therefore, quality rather than the quantity of dietary fat and carbohydrates are important.

Disclosure

The author reports no conflicts of interest in this work.

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