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Diabetes & its Complications

Evolutionary Origins of Diabetes Mellitus

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ABSTRACT

Diabetes became a global pandemic within only a few decades, and is now ravaging both the developed and developing worlds. Physicians, while competing with this "new" challenge are focusing mostly on the serum blood levels and diabetic complications; and in the best case, to the proximate causes of the disease such as obesity, family history, age and diet. The ultimate causes of this condition, like any other civilisation disorder, lay in the evolutionary history of the human. A number of hypotheses put forth to explain the exponential increase of the diabetes prevalence with an evolutionary point of view such as; evolutionary trade-offs, developmental plasticity, thrifty genotype, life history and selfish brain alongside with the disrupting change in human diet. Finally, four main interacting predisposing factors to consider in planning the diabetes control activities are prominent: Genes, prenatal environment, diet and physical activity. If the former two are difficult to act on, the latter two need to be introduced in the agenda of all the parties.

Keywords

Diabetes, Diet, Evolution, Hypotheses.

Introduction

Diabetes mellitus (DM) has burst; the global prevalence of diabetes increased from 211.2 million (196.0–228.5) in 1990 to 476.0 million (436.6–522.8) in 2017. It is estimated that the number of diabetics will reach up to half a billion in 2030 [1]. Diabetes mellitus, is a disease which can almost completely be avoided; however, while the humans were unaware of it throughout their evolution, today DM has become one of the most common diseases in the world [2]. Why humans have diabetes mellitus can not only be explained with the cellular and genetic mechanisms which underlie the disease; it lies much deeper: Diabetes mellitus is a growing problem, because the human body has been exposed to conditions which are way more unusual than the conditions it is adapted to; it is coping with problems like modern diets and sedentarism [3]. During millions of years, evolution has selected ancestors who killed each other for nutrients like simple carbohydrates rich in energy and who stored the excessive calories as fat. These distant ancestors of ours did not have the opportunity to muddle around all day long and consume cupcakes and sweet beverages [4].

Evolution, is the process of development of different organisms out of their previous forms. It can also be defined as the alteration of in-group gene density in time. Evolution works with the selection of phenotypic diversification, namely by means of the genotypes that produces them. The characteristics of living organisms are transmitted from one generation to the other with two contrasting tendencies; tendency of preserving its core and tendency of diversification [5]. Evolution theory analyses the roles of, 1-environmental adaptation and 2-genetic variation in a reproducing population in speciation; explaining them by virtue of giving reference to a very simple process of natural selection; namely, the differences in survival and reproduction potentials [6]. The functioning of evolution is scratchy. If the existing material works -for the time being-, the genetic heritage continues; indeed, there exists nor will exist any organism which came close to being perfect. Evolution is a bundle of trade-offs; it can be harmful for one feature while developing another. Thus, while specialties with advantages are selected and favoured, they carry along specialities with disadvantages or which are neutral. So, because of these constraints and as a result of the inevitable trade-offs, the offspring invests in reproduction rather than health. The human body is not "designed" in a way which functions optimally; it has been evolved with compromises which obligate trade-offs that increase the

risk of a series of developmental, biophysical and psychological deteriorations [7].

Trade-offs

Trade-off is a natural selection process which increases the performance in one domain (reproduction) while decreases it in another domain (survive form the predators). As longevity and post-reproductive period string out, some of the diseases do not diminish; because the selection pressures weaken. Fitness can be gained by means of cumulative reproductive success of all the stages of our individual life histories. Reproduction participates more to early life fitness. Juvenile fitness compounds like the duration of reaching the fertile age and fecundity, effect morbidity and mortality in elder years through trade-offs. If these trade-offs are the results of the same active genes during both the early and late stages of life, even though the selection of juvenile characteristics affect fitness negatively in elder stages, the prevalence of these genes within the population increases. This genetic effect is called 'antagonistic pleiotropy': It can be described as 'the exposure of the organism to both the positive and negative effects of a single allele [8]. One example of a developmental trade-off which causes disease in elder ages is the increase of tendency to metabolic syndrome in elder ages due to the deceleration of growth and malnutrition during fetal growth and/or early childhood. In late childhood when better nutrition conditions are met, catching-up the deficient body weight too quickly may be also harmful in the following years. The metabolic syndrome which emerges in adulthood, is the price we pay for rapid growth following the nutrient stress during young ages. Deficient nutrition during prenatal period is related to diabetes mellitus risk in adulthood through insulin susceptibility [9].

Thrifty genes

Thrifty genotype hypothesis was asserted to explain growing diabetes incidence in the Western World. According to this hypothesis, the thrifty genes, which encourage the body to store the body fat efficiently, were advantageous during the early stages of our evolution because they helped their owners to survive during famine periods. However, in the modern society these genes encourage the storage of redundant fats and have become disadvantageous. These disadvantages are manifested as obesity and diabetes [10]. Human communities have been exposed to nutritive stress both prior and post agricultural revolution, thus a "thrifty" metabolism may have been positively selected. The metabolic basis of this thrifty genotype may be related to selective insulin resistance. The phenomena related to fat storage also work this way. Diets rich in saturated fats, poor in fibre and energy-dense, increases insulin resistance together with physical inactivity. Thus, the critical components of Western lifestyle plays a role that favours insulin resistance and weight gain. In conclusion, the thrifty phenotype is a basic predisposing factor in diabetes mellitus [11].

Adipose tissue and pro-inflammatory genotype

Insuline resistance is also related to a pro-inflammatory thrifty genotype. The pro-inflammatory molecules produced by the adipose tissue plays an active role in the development of insulin resistance. Free fatty acids cause low-level inflammation in skeletal muscles and the liver. In this way, high levels of free fatty acids caused by obesity and fatty food, provoke low-level inflammation in skeletal muscles and the liver, thus insulin resistance [12]. In the struggle with infections, emergence of processes like inflammation and fever necessitates a high metabolism. In order to maintain this infective situation, it needs adipose tissue. In this respect, the adipose tissue is considered as an assistant protector against infectious diseases. As a result, active immunity can be the ancestor of type 2 diabetes. Chronic diseases which are the products of our proinflammatory design have increased throughout our evolution [13]. Thanks to our thrifty genotype, we have developed a low level, chronic and systemic inflammation state which is encouraged by proinflammatory cytokines and adipocytes. Moreover, the changes which occur in our innate immune system due to our proinflammation genotype are related to insulin resistance and diabetes [14].

Developmental plasticity

In the early years of life, beginning from the womb to the age of reproduction, individuals with similar genes, produce different phenotypes as an answer to different environmental conditions; this is called 'developmental plasticity'. Developmental plasticity emerges as a result of the interaction between the developing organism and the environmental conditions in which this organism lives. People who have suffered from in utero starvation, develop obesity, heart diseases and schizophrenia in higher levels during adulthood compared to their peers who grew up under better conditions. Children who experience negative psychological events exhibit more psychological weariness and have a shorter life span compared to their peers [15-18].

Life History

Life history, describes how one's life cycle -from the zygote to death- is designed by natural selection, in order to secure reproduction against the pressures caused by the environment. An optimal life history program should maximise the total energy allocation to reproduction. Living beings increase their fitness investing either in the timing of mortality or fertility. The variances that emerge during mortality and/or fertility, effect "inclusive fitness": Increase in mortality and/or fertility can be seen directly on the individual, his/her child or a relative. Trade-offs that occur during resource channelization, have opponent effects in terms of mortality and fertility: Increasing fertility through increasing the mating frequency shortens the life span by compromising immune functions. The energy allocation to growth decreases fertility in juvenile ages but later on increases fertility. Resource allocations, for example feeding for the viability of the offspring, either decreases parental fertility or shortens their life span [19,20].

Civilisation disorders

In today's rich countries human health has overtaken the Stone Age in many aspects. Infant mortality, infectious diseases and traumatic injuries used to be much more frequent in those ages. However,

the discrepancies between today's life style and that of the pre-agricultural humans, provide the basis for chronic degenerative diseases which are the primary reasons of mortality in Western countries today. These civilisation disorders are indeed not new; diabetes has been diagnosed two thousand years ago. However, the dominant life style of today's industrialised Western countries have doubled the prevalence of this health condition. Diabetes was very rare amongst American-Indians until 1900's, whereas today Pima natives are the World premieres of diabetes mellitus [21-24].

Selfish Brain Theory

Selfish brain theory can be the determinant of evolution of insulin resistance. The brain, even though it constitutes only 2% of our total body weight, consumes 50% of the body glycose. The energy of the brain depends solely on glycose and consumes more than 20% of the glycose the body consumes during rest. The brain activates stress mechanism through hypothalamic-pituitary axis and autonomous nervous system against rivals like fats and muscles, thus provides itself a stable and abundant glycose resource. Activation of the sympatho-adrenal system, inhibits the intake of glycose by the nearing tissues by releasing insulin through inducing insulin resistance and increasing hepatic glycose production. Moreover, the brain procures its glycose reserves before other organs consume it [25,26].

Evolution of our diet

The diet of our ancestors living in the African jungles was composed of leaves, roots and fruits. The glycemic index of the consumed carbohydrates were low and they necessitated high physical activity to be obtained. When the climate got colder, these jungles turned into dry savannahs. This urged our ancestors to migrate towards the sea coast. In this way, their diet turned into low carbohydrate, high protein and iron, retinol, zinc, vitamin 12 and unsaturated fish oil when they began hunting big animals. These new components of the pre-human diet, apart from procuring more energy, also accelerated encephalisation and enabled the development of intellectual capacity [27].

Gastrointestinal hormones like leptins, may be referring to an evolutionary adaptation. Leptin passes through the blood-brain barrier and informs the brain on the nutritive condition of other parts of the body. Hypertriglyceridemia which emerges during starvation periods, inhibits leptin transmission. Thus, during starvation periods, leptin inhibition may have provided an advantage for survival. Potential leptin inhibitors should be affecting neurogenesis and the consciousness. Therefore, insulin resistance should be selected during evolution in order to prevent the brain from lack of glycose. In order to overcome the metabolic price of encephalisation, decreasing other tissues metabolic rates should have been selected. The diet composed of high protein and low carbohydrates during the Ice Age, should have promoted selection of insulin resistance, increase of hepatic glyconeogenesis and decrease of peripheral glycose intake [28].

Insulin resistance is the case where insulin is not capable of showing its plasma glycose decreasing effect. Insulin resistance is the relation between metabolic syndrome, glycose intolerance, hypertension and dyslipidaemia and is directly related to cardio-vascular diseases. As a result of insulin resistance, hyperinsulinemia, shows an anabolic effect on lipid metabolism and causes obesity; in the adipocytes, lipogenesis accelerates while lipid catabolism decelerates and thermogenesis decreases; thus, muscle mitochondrial oxidative capacity increases [29].

With the development of intelligence, our ancestors left Africa; by the river banks they came across vegetables and cereals, as well as cattle, goat, sheep and wild boar. They domesticated these animals, thus their nutrition changed from wild weed to cereals and their subcutaneous fat tissues thickened, muscles fattened and began storing Omega-6. And our ancestors began reproducing by choosing fatty animals for the sake of their taste. This increased the saturated fatty acids in products like milk. Usage of these animals' skins as garment, resulted in negative selection of adaptive thermogenesis. Obesity emerged as a result of the decrease of fat consummation of the human body which heated with fur [30].

With the industrial revolution, cereal consummation increased, thus the components of our diet changed significantly. Over processed cereals which took the place of lamellar green plants, enriched our diet in terms of carbohydrate and omega 6 fatty acids, however impoverished it in terms of omega-3 and antioxidants. Refined sugar was abundant and it increased postprandial hyperinsulinemia; and this increased the negative effects of insulin-resistant genotype. Saturated fatty acids, omega-6 trans fats took the place of unsaturated fatty acids and omega-3. Sodium consummation also increased rapidly, causing lack of potassium, complex carbohydrates and food with fibre. Decrease of omega-3, while omega-6 increased in our diet, resulted in the increment of metabolic products which cause insulin resistance [31].

Conclusion: The diabetes mellitus

The "agent pathogen" of modern diabetes mellitus is the Western lifestyle. The diabetes mellitus prevalence seen amongst the adult members of today's industrialised countries is almost 10-20 times the rate seen amongst hunter-gatherer societies. As consummation of healthy products decrease throughout the World, as we adapt more the sedentary life style and as our life span lengthens, adult diabetes began to be frequent in places where it has not been seen before. Today majority of the adults with diabetes are from Southeast Asia [32]. Diabetes mellitus-specific mortality rates in Western countries increased 10 fold amongst the people over 45 years old between the last quarter of 1800's and the first quarter of 1900's [33]. Because we do not succeed in protecting ourselves from the risk factors of this disease, the prevalence increases from one generation to another. Similar increments were observed amongst preliterate communities who immigrated from developing countries to industrialised ones. Migration of these groups to developed countries resulted in a rapid change in their lifestyles. The most common health conditions observed amongst the members of these groups are obesity and maturity onset diabetes of the young (MODY): MODY refers to any of several

hereditary forms of diabetes mellitus caused by mutations in an autosomal dominant gene disrupting insulin production [34,35].

This pandemic has not developed in a neutral way; regardless of the lifestyle factor, it hits some populations more severely: The chance of a Hispanic living in USA to develop diabetes mellitus is two times more than of a white American [36]. Recently a gene which will help us explain the diabetes mellitus risk difference between different populations. The gene variation in question can be traced back to our neanderthal ancestors. In order to explain the fact that the gene which inclines us to diabetes is very old and why it does not exist amongst Africans, it is assumed that this gene variation was not evolved in our lineage but that of the neanderthals and that we inherited most of these mutations from the Neanderthal lineage. Hybridisation of the sapiens and the neanderthals, may have resulted in the transmission of the gene variation related to diabetes to sapiens lineage [37,38]. This gene, encodes a protein which activates some lipids in the liver cells. The version of this gene which predisposes diabetes mellitus, are different from the standard gene variation in five different mutations; each one of these mutations spoil the function of the encoded protein enough to develop diabetes. The mutated version of the gene, increases the chance of its carriers to develop diabetes mellitus in a young age without developing obesity at the same time and is observed more frequently in some populations. The chance to carry at least one mutated gene copy is 50% in native American descendent Hispanics, while it is not seen at all in Africans [39].

Diabetes mellitus too, like obesity, is an interrelated disorder group; each of these disorders derives from the interaction between genetic and environmental factors. Lifestyle in industrialised countries empower these factors through several mechanisms in a way which encourages the emergence of MODY diabetes: First mechanism is the strongest diabetes mellitus risk factor, namely obesity. Cellular insulin receptors of the people with obesity in western countries are low. As a result, they exhibit a relative tissue resistance against insulin, thus the blood-insulin levels remain high. Second, high physical fitness is more frequent in preliterate societies, increases the insulin receptors and causes the insulin to bond more; thus, the insulin susceptibility of the body remains high. In hunter-gatherer societies serum insulin levels are low, because physical fitness increases cellular insulin susceptibility. Third, over consummation of fibres and complex carbohydrates which are poor in nutrition, decrease the levels of fasting and postprandial serum glycose. This type of diet, constitutes the foundation of the daily nutrition in hunter-gatherer societies; Western lifestyle is completely unusual to that. That's to say, including the foods based on olive oil of the Mediterranean cuisine will be preventive against diabetes [40,41].

Diabetes mellitus, is a disorder which derives from the incompatibility between our modern lifestyle and the metabolism of our evolutionary history, which necessitated intensive physical activity in order to survive in an environment where the food was scarce. In this challenging environment, even the carriers of genes which enabled diabetes, were not able to develop diabetes even though when they had abundant food and opportunity to rest [42]. This fact is enough to explain why these genes are frequent today; these genes have never been exposed to the fury of natural selection in any stage of our evolutionary history, thus became harmful to human health only recently. Therefore, it is important to comprehend the ultimate causes, not only the proximate mechanism, in order to prevent a complex problem [43]. If excessive visceral fat provokes the insulin resistance underlying type 2 diabetes, we can understand why this disease is completely evitable and why numerous interrelated factors incline some people and protect the others [44]. We cannot control two of these factors: Genes and prenatal environment. The two others, diet and activity, are more important factors that designate energy balance and we can have control over them [45,46].

Although the awareness about the ultimate/evolutionary causes of diseases is not lifesaving, knowledge or even intuition of evolutionary origins of the current discomfort may help both the health care professionals and patient to handle it easier.

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