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Mini Review

Nontraditional Approaches for the Management of Metabolic Risks

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Abstract

Large population studies have indeed indicated that metabolic risks have their origin during early developmental stages and childhood. Altered metabolism, endocrine disruptors, and environmental and epigenetic factors, may contribute to the development of metabolic diseases such as hypertension, excess weight, obesity, endothelial dysfunction, subclinical atherosclerosis, and type-2 diabetes. The definition and classification of diabetes mellitus and various tests used for its diagnosis, were put together by the National Diabetes Data Group of the USA and World Health Organization's Expert Committee on Diabetes Mellitus, in 1979 and 1980. The diagnostic fasting plasma (blood) glucose value has been lowered to ≥ 7.0 mmol l-1 (6.1 mmol l-1). Impaired Glucose Tolerance (IGT) is changed to allow for the new fasting level. A new category of Impaired Fasting Glycaemia (IFG) is proposed to encompass values which are above normal but below the diagnostic cut-off for diabetes (plasma ≥ 6.1 to < 7.0 mmol l-1; whole blood ≥ 5.6 to < 6.1 mmol l-1). Gestational Diabetes Mellitus (GDM) now includes gestational impaired glucose tolerance as well as the previous GDM. A study done in 26 industrialized nations reports a significant decline in the deaths related to cardiovascular disease (CVD), whereas the same study reported an increase in the deaths associated with diabetes. In spite of the fact, that these studies reported a decline in the CVD-related deaths, CVD has remained as the number one killer for the past 100 years. These observations make one wonder, about what is happening when it comes to the prevention of metabolic diseases worldwide. Western medicine is disease-centric and has done well in the diagnosis of the risk factors and management of observed risks. However, they have done very little in reduction, reversal or prevention of metabolic risks and resulting increase in metabolic diseases. According to various global experts, excess weight, obesity and type-2 diabetes have increased to epidemic proportions worldwide. No country has reduced or reversed this trend in the increase of metabolic diseases. In this overview, we would like to discuss and present our views, on some nontraditional approaches to the management of metabolic risks, metabolic diseases, and diabetes.

Keywords: *Metabolic Risks; Obesity; Endothelial Dysfunction; Type-2 Diabetes*

Introduction

This year the American Diabetes Association (ADA) is celebrating its 75th anniversary. According to their report, it was started with 26 clinicians, and since its beginning, has grown to include a million volunteers. Diabetic mellitus is a group of metabolic disorders in which, there are high levels of glucose in the blood for over a prolonged period. Historically speaking, it is one of the earliest metabolic diseases described. Egyptians as well as Indians, knew about excess sugar in the urine as early as 1500 BC [1]. In spite of this awareness, increase

in the incidence of these clusters of metabolic diseases, have not been reduced or reversed in any country. On the other hand, according to Global health reports, the excess weight and obesity, has increased two-fold and type-2 diabetes four-fold worldwide (since 1980), in the last three decades [1-10]. What are metabolic risks? What are metabolic diseases? How best can we manage these observed risks, and slow down these epidemics? In view of the fact, that we are going to be discussing metabolic risks and metabolic diseases, let me start with a brief introduction to metabolism. In brief, metabolism is the chemical process your body uses, to transform the food you eat into the fuel, that keeps you alive and well. Diet and nutrition by and large, consists of proteins, carbohydrates, fats and a variety of micronutrients. These substance's when ingested are broken down by enzymes in our digestive system, and then carried to the cells, where they can be used as fuel. The body either uses these metabolites immediately, or stores them in the liver, body fat, and muscles for later use. A metabolic disorder occurs, when the metabolic process fails, and causes body to have either too much or too little of the essential metabolites needed to stay healthy. All the known metabolic risks, such as excess weight, hypertension, endothelial dysfunction, subclinical atherosclerosis, obesity, and type-2 diabetes, have reached epidemic proportions worldwide [11-15].

In spite of the fact, that there are a variety of known metabolic risks, that promote development of type-2 diabetes, when it comes to the management of this disease, clinicians rely only on the management of blood levels of glucose in the developing countries. The American College of Physicians (ACP), has published the most recent guidelines in April of this year [16]. According to these guidelines, clinicians should aim to achieve an HBA1c between 7% and 8% in most patients with type-2 diabetes. The very purpose of management of diabetes, is to prevent the clinical complications associated with this disease, such as retinopathy, neuropathy, nephropathy, and various vasculopathies. Studies have not consistently shown that intensive glycemic control of HBA1c levels below 7% reduces clinical microvascular events, such as loss or impairment of vision, end-stage renal disease, or painful neuropathy, or reduce macrovascular events and death [16]. According to a study by Cesare and associates, between 1980 - 2009, cardiometabolic mortality declined in all the 26 industrialized countries studied, whereas, diabetes-related mortality increased in high-income countries. These results indicate, the contributions of modifiable risk factor and its management in reducing CVD mortality. Having said that, I would like to inform the readers, that in spite of this observed decline in CVD mortality in industrialized countries, cardiovascular disease still ranks as number one killer worldwide. In a recent article, I discussed the early diagnosis of the risks, and management of observed risks as a means, to reduce deaths due to cardiometabolic diseases [17]. In this mini overview, we will discuss some metabolic risks, that promote pathophysiology of metabolic diseases, and present our views, on the development of novel approaches, with complementary therapies for the known risks, as well as for some less known risks [17,18].

Discussion

When it comes to the diagnosis of the diabetes in the general population, family history is associated with higher risk for prediabetes [19]. If the fasting glucose is 100 to 125/dl, then one is considered to be prediabetic, or one with impaired glucose tolerance. In countries like India and China with huge populations, it is rather difficult to screen general population for the early detection of prediabetes. According to the Center for Disease Control (CDC) and Prevention, 37% of US adults older than 20 years and 51% of those older than 65 had prediabetes in 2009 - 2012. This data when applied to the entire population, translates to 86 million adults with prediabetes in the United States alone (Personal observations). This data also suggests, that there are more prediabetics than diabetics in any given population. If we consider India and China, with 75 million and 115 million diabetics, then the estimated prediabetics will be equal to that number are more (Personal observations). The reason we are mentioning this fact is to illustrate, that globally the entire prediabetic population, which is greater than the known diabetic population, is left undiagnosed and as such untreated.

Meta-analysis of several studies on prediabetics, have shown an increased risk of all-cause mortality [20]. Prediabetes involves multiple factors including genetics, gene expressions, epigenetics, peripheral insulin resistance, defects in insulin secretion, glucotoxicity,

lipotoxicity, impaired incretin release, amylin accumulation, inflammation, oxidative stress, and decreased β-cell mass leading to β-cell dysfunction [21]. Although several biomarkers have been reported for diagnosis of prediabetes condition, in our opinion, just a glycated hemoglobin or glycated albumin screening is sufficient to identify prediabetes. Having said that, we want to remind the readers that even in industrialized countries, there exists no universal screening for the diagnosis of prediabetes. Medical cost analysis associated with prediabetes, recommends, lifestyle interventions to prevent or delay the development of diabetes [22]. What are some of the options for the early diagnosis and prevention of these chronic disorders? In our earlier articles, we have articulated that understanding the mechanism of disease, is a better option for the development of preventive strategies. To illustrate this point, we will present a metabolic risk, that is very well investigated and is preventable.

The low-birth-weight (LBW), remains a high risk for infant mortality (NEJM 312:82-90, 1985). Collaborative Studies in India, from Medical Research Council (MRC) of United Kingdom (UK), with Mission Hospital Mysore (MHM), and King Edward Memorial (KEM) Hospital, Pune, have demonstrated that over a third of all babies born in India, are of low-birth-weight [23-25]. Follow up of these LBW babies to their adult hood, have demonstrated that they develop a significantly high incidence of elevated blood pressure, obesity, diabetes (type-2) and cardiovascular diseases (CVDs). In view of these findings, MRC has set up an epidemiology resource center at KEM hospital Pune and at Mission Hospital, Mysore, India. In India close to 17 million babies are born per year. Thirty percent or more of these babies, are of low birth weight and are "at risk" for developing cardiometabolic diseases. This is not a finding that is unique to the South Asians. Xiao., *et al*. in Peking, studied individuals born between 1921 to 1954 at the Peking Union Medical College Hospital, to estimate the association between birth weight and Metabolic Syndrome [26]. In the 1980s Barker developed a hypothesis according to which, many nutritional events that occur during the intrauterine growth, will influence the development of adult diseases [27,28]. Harvard researchers found, that multiple micronutrient supplementation was more effective, than iron and folic acid supplementation, at reducing the risk of low birth weight [29]. These findings illustrate, that there is a great window of opportunity to develop complementary therapies, to reduce or prevent the development of metabolic diseases.

In view of the fact, that KEM Cohort in Pune, India, has been studied extensively for several decades, we initiated a bilateral study between the researchers at the Children's National Medical Hospital, Washington DC and the staff at the Diabetes clinic, KEM Hospital, Pune, India, to explore molecular mechanisms involved in the fetal origin of adult diseases. Dr. Robert Freishtat and associates at the CNMH, Washington DC, have demonstrated, that visceral adipocytes shed exosomal-mediators (microRNAs) predicted to regulate key end-organ inflammatory and fibrotic pathways [33]. Preliminary studies between these two institutions, have been encouraging, and we are seeking funding from the prestigious National Institutes of Health (NIH) USA, for further studies on this important topic. Yet another molecular mechanism, that can predict the development of type-2 diabetes is profiling of plasma free amino acids (PFAA). Several studies have consistently demonstrated, that increased levels of plasma and urinary branch chain amino acids (BCAAs), are associated with insulin resistance and have the quality to predict diabetes development [30-33]. Micronutrient-deficiency can be treated, by dietary supplements and used therapeutically as shown in the Harvard studies. However, the emerging technologies demonstrating molecular markers like exosomes (miRNAs), and plasma free amino acids are futuristic, waiting for further development for therapeutic applications.

Diabetes to a great extent, is a response to the excess sugar in the blood. The source may be direct sugar, or sugary drink consumption, or eating refined carbohydrates [34]. Irrespective of how the sugar level goes up in the blood and tissues, there seems to be an increase in inflammatory markers, insulin resistance, and LDL-cholesterol. Consuming 50 grams of fructose, seems to induce a spike in inflammatory markers like C-reactive protein (CRP), just 30 minutes later [35]. The increased CRP level, seems to remain high for two hours [36]. Several studies suggest, that carbohydrate nutrition is related to oxidative stress and inflammatory markers-Nf-kB [37]. There is considerable evidence, to suggest an important role for the overproduction of reactive oxygen species (ROS), in the pathogenesis of vascular diseases. These ROS can be released from nicotinamide adenine dinucleotide oxidase, xanthine oxidase, lipoxygenase, mitochondria or the uncoupling of nitric oxide synthetase [36,37].

The transcription factor Nrf-2 (nuclear factor, erythroid-2-related factor-2, Nrf-2) for instance, a master regulator of detoxification, anti-oxidant, anti- inflammatory and other cytoprotective mechanisms, is raised by health promoting factors. This transcription factor, activates the transcription of over 500 genes (so called survival genes) in the human genome, most of which have cytoprotective functions. The most healthful diets such as Mediterranean and Okinawa are rich in Nrf2 raising nutrients. Recent studies however, have demonstrated that induction of Nrf2 and Ho-1 expression by Protandim (a mixture of five phytochemicals; Ashwagandha, Indian Bacopa, Indian Green Tea, China Milk Thistle and China Turmeric) is associated with a reduction in oxidative stress and fibrosis, preservation of the right ventricular (RV) microcirculation and RV function [38]. Studies by the pioneer scientist, professor Joe M McCord and associates on the effect of Protandim on various pathways have shown, significant modulation by Protandim not only of pathways involving antioxidant enzymes, but also those related to Colon Cancer, Cardiovascular disease and Alzheimer's disease [39,40].

Metabolic disorders including obesity, type-2 diabetes, and atherosclerosis, have been considered lipid storage disorders [41]. We have discussed above, the ill effects of over nutrition, whether it is sugars or carbohydrates, and how excess substrates induce acute as well as chronic oxidative stress and inflammation. It is widely known, that the chronic low-grade inflammation, plays a key role in the initiation, propagation, and development of metabolic diseases including diabetes. The transcription factor NF-kB promotes immunity by controlling the expression of genes involved in inflammation. Similar to the studies on the transcription factor Nrf-2, studies can be designed to develop complementary therapies, for the reduction of chronic and acute inflammation. One way to combat this situation is, to promote the development of anti-inflammatory cytokines. Blocking the action of inflammatory mediators, is considered as an attractive therapeutic approach. In our opinion, there is a window of opportunity, to develop complementary therapies to modulate, oxidative stress and inflammatory pathways. There are reports attributing beneficial effects of Omega-3-fatty acids, curcumin, various antioxidants, and phytochemicals.

Authors of a recent study concluded, "We demonstrate for the first time in humans, that a single high fat meal can induce pathological red blood cell (RBC) remodeling and induce oxidative stress, in conjunction with elevations in plasma and RBC-bound myeloperoxidase". These authors further speculated, that consumption of heavy meals enriched with fats may promote destabilization of vulnerable atherosclerotic plaques, leading to acute myocardial infarction [42]. According to Minnesota researchers, even in children, oxidative stress and adipokine levels, worsen throughout the continuum of obesity. Kelly and associates in Minnesota, conducted a study to assess subclinical inflammation, fasting insulin, and endothelial dysfunction, before and after exercise in overweight children. Just eight weeks of moderate exercise, improved fitness, HDL-cholesterol, and endothelial dysfunction [20]. Our own studies in India, demonstrated the beneficial effects of oral supplementation of l-arginine, a substrate for Nitric Oxide synthesis, in improving endothelial dysfunction and lowering overall cardiometabolic risk score [18,43].

Glycated hemoglobin for decades, has been the gold standard for the management of patients with diabetes. This is not the only protein that is glycated, other glycated proteins include, fructosamine, glycated albumin and advanced glycation end products (AGEs) (Clin. Lab.Med.21:53-78, 2001). Increased amount and duration of glucose in blood, allows more glycosylation to occur not only hemoglobin, but other proteins as well. Excess glycation of important protein amino groups, affects cell function and may create cell destabilization. This metabolic alteration seems to target organs and tissues, that do not depend on insulin for their absorption, such as kidneys, blood vessels, peripheral nerves, and lenses of the eye. In view of these observations, there is some interest in the development of potent inhibitors of aldose reductase, oxidative stress, and antioxidants as therapeutics. It is believed, that excess of plasma vitamin C can compete with glucose, in binding with hemoglobin and protein amino groups. Having said that, we feel that there is great need for additional research on the role of glycation of proteins and the mechanism by which glycated proteins modify the physiology and function of some cells. In spite of the fact, that there is abundant literature on glycated proteins, we know very little about their role in diabetes related clinical complications. According to a new study in the journal of Diabetes Care, there does not appear to be a critical association between HBA1c and wound healing in patients with diabetic foot ulcer [44].

Studies from Professor Roy Taylor and associates at the University of Newcastle, UK, have demonstrated the reversibility of diabetes by low calorie diet. It has been shown that, within a week either by negative calorie balance or by bariatric surgery, fasting glucose can be normalized [45]. Author concludes, "Type-2 diabetes has long been regarded as inevitably progressive, requiring increasing numbers of oral hypoglycemic agents and eventually insulin (usual therapeutic approach), but is now certain that the disease process can be halted with restoration of normal carbohydrate and fat metabolism. Type-2 diabetes can be understood as potentially reversible metabolic state, precipitated by the single cause of chronic excess intraorgan fat". The diet used in this seminal study is as follows:

- 3 diet shakes per day and 240 grams of non-starchy vegetables taken in between 600 and 700 kcal a day for 8 weeks.
- Volunteers then gradually returned to eating normal food over the next two weeks with very careful instruction on how much to eat.
- Volunteers were seen once a month and supported with an individualized weight maintenance programme over the next 6 months.
- To keep weight steady after the weight loss, they were eating around one third less than before the study.

In view of the fact, that low calorie diet (low carbohydrate), seems to reduce or reverse diabetes, there is renewed interest in Ketogenic diets. Ketogenic diet could be an alternate way to weight loss, however, it is hard to follow. The diet is also heavy on red meat and fats. Some recent studies suggest, that it may even promote insulin resistance. In a recent article I wrote, "you are what you eat". In the recent issue of the journal Circulation, authors remind us, about the common recommendation, "Eat a variety of foods" or the importance of dietary diversity. In view of the fact, that there is no standardized measure for dietary diversity, by and large it is recommended, that people should have adequate intake of plant foods, protein sources, low-fat dairy products, vegetable oils, nuts, limited consumption of sweets, sugar-sweetened beverages and red meats [46].

An emerging area of great interest for researchers, studying metabolic risks and metabolic disease, is the discovery that the microorganisms comprising the gut microflora, are now considered a metabolic "organ", modulating multiple functions of the host [47]. Our gut microbiota, contains tens of trillions of microorganisms, including at least 1000 different species of known bacteria, with more than 3 million genes (150 times more than human genes). Some of the recent studies have described mechanisms, that contribute to the development of obesity and associated metabolic disorders [48]. Several reports have indicated, that *Akkermansia muciniphila*, a beneficial bacterium in our guts, affects glucose metabolism, lipid metabolism, and intestinal immunity, and that certain ingredients such as polyphenols, may increase the abundance of *Akkermansia muciniphila* in the gut [47-51]. We discussed earlier in this article, that the branch chain and aromatic free amino acids in the plasma, as predictive of future diabetes. It has been shown in some studies, that altered microbiota can indeed modulate the levels of these essential amino acids. Like precision medicine or personalized medicine, further research is needed to establish, whether these kinds of personalized approaches to modify gut microflora favorable to health are feasible.

Conclusions

Framingham Heart Study group, which was initiated 70 years ago, by the prestigious National Institutes of Health (NIH) USA, and the Boston University School of Medicine (BUSM), developed a list of modifiable risks, that promote cardiovascular diseases. Several studies since then, have shown that managements of these modifiable risks, have contributed significantly, to the decline in deaths due to CVDs worldwide. However, there seems to be no such observed decline in the morbidity and mortality, related to type-2 diabetes. In fact, no country has reduced or reversed the rate of increase of metabolic diseases in the last three decades. In majority of the countries, standard diabetes care seems to be, treatment of patients with oral hypoglycemics and then follow with insulin therapy, when oral medications fail or become inadequate. In recent articles, we have advocated that it is better to treat the disease, rather than to focus on just the management of risk factors. We have discussed in this overview, early risk factors for the development of metabolic diseases starting from the

time of conception. We have pointed out that nutrient-deficient diet may contribute to altered metabolism. We also have discussed childhood obesity, oxidative stress, inflammation, endothelial dysfunction, and subclinical atherosclerosis, as possible causes of observed metabolic risks. We have briefly discussed the dietary role as well as the contribution of the gut microbiota, in promoting altered metabolism. In view of the fact, that all the metabolic diseases, such as hypertension, excess weight, obesity, metabolic syndrome, and type-2 diabetes have reached epidemic proportions, we have initiated a dialogue with the scientific and medical community, to think "out of the box", and develop novel approaches to the management of metabolic risks, to reduce the incidence of metabolic diseases worldwide. Purpose of this mini review was not to discuss diabetes management, but to elaborate on the metabolic risks, that promote the development of metabolic diseases, including type-2 diabetes. In a short review like this, it is hard to cover all aspects of metabolic risks, readers are urged to refer to original articles for additional information [52-65].

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