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Potential Nutrigenomic Approaches to Reduce the High Incidence of Obesity in Qatar

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Abstract

Obesity prevalence has been growing exponentially over the last few decades, with a high impact in high-income countries, like Qatar. Several approaches are attempting to understand the causes of this phenomenon however more important is what to do to reverse the trends. Obesity is widely studied, mostly in Europe and the Unites States, and a number of studies have demonstrate the role of specific gene patterns, transcriptome and proteome pathways, and gut microbiome strains. The Omics sciences have a great potential to investigate the determinants of non-communicable diseases, such as obesity. Nutritional genomics sciences apply all the Omics approaches to address nutrition-related diseases, investigating the interaction between genes and diet. To date, few data are available from nutrigenomic studies conducted in Middle East and particularly in Qatar to help the design of targeted interventions. The high incidence of obesity and the peculiar genetic make-up of the Qatari population provide opportunities for exploring nutrigenomic approaches to help addressing the problem.

Keywords: Nutrigenomics; Obesity; Qatar

Abbreviations

NCDs: Non-Communicable Diseases; WHO: World Health Organization; BMI: Body Mass Index; CVD: Cardiovascular Disease; T2DM: Type 2 Diabetes Mellitus; GWAS: Genome Wide Association Study; OMIM: Database Online Mendelian Inheritance in Man; BAT: Brown Adipose Tissue; WAT: White Adipose Tissue; NAFLD: Non-Alcoholic Fatty Liver Disease; NGS: Next Generation Sequencing; SCFAs: Small Chain Fatty Acids; GABA: γ-Amino Butyric Acid; TLRs: Toll-Like Receptors; LPS: Lipopolysaccharides; QF: Qatar Foundation; QNRF: Qatar National Research Fund

Introduction

Obesity, diabetes, cardiovascular diseases, and other non-communicable diseases (NCDs) account for more than 60 per cent of annually global deaths [1], and this is estimated to increase exponentially by 2025. The World Health Organization (WHO) defines as overweight a body mass index (BMI) ≥ 25 kg/m^2, and as obesity a BMI ≥ 30 kg/m^2 [2,3]. The global prevalence of the overweight and obesity is on the rise, as demonstrated by the first Global Burden of Metabolic Risk Factors of Chronic Diseases in 2008 [3], and confirmed by the Global Burden of Disease Study 2013. The first study analyzed data from 199 countries and territories and 9.1 million adults with respect to the prevalence of overweight and obesity between 1980 and 2008 [3], and demonstrated that the prevalence of obesity nearly doubled worldwide during that 28-year period (about 34% overweight and 12% obesity). More recently, the analyses for the Global Burden of Disease Study 2013 [4] further documented that worldwide, the proportion of adults with a BMI of 25 kg/m^2 or greater increased between 1980 and 2013 from about 29% to 37% in men and from about 30 to 38% in women. Since 2006, the increase in adult obesity seems to have leveled off in several high-income countries, but the incidence generally remains higher than in most low- and middle-income countries [5] (Figure 1A).

Obesity in Qatar

The Middle East has a peculiar demographic pattern and environmental characteristics reflective of an obesogenic environment. The Middle East also has the highest prevalence of obesity in relatively high-income economies (Figure 1B). BMI is considered the most relevant risk factor for NCDs and high BMI frequency is duplicated in the decades 1990 to 2010 in the high-income Arab countries, explaining the increase in NCDs as causes of death [6,7]. In the Qatari context, between 2004 and 2010, the top four NCDs causes of death in Qatar were: circulatory disorders; cancers; endocrine, nutritional and metabolic disorders; and respiratory diseases. The distributions of deaths from these major causes in 2012 were as follows: circulatory, 18.3% total (20%, Qatari population); neoplasms, 16.1% total, (21.6%, Qataris); endocrine and metabolic, 9.9% total, (14.1%, Qataris); respiratory, 5.5% total, (7.5%, Qataris) [8]. Diabetes accounts for a very high proportion of the 14.1 per cent mortality from endocrine, nutritional and metabolic disorders. NCDs are the main cause of death in Qatar [9]. Health statistics reveal that, in 2010, the total deaths in Qatar among the different age-groups due to NCDs was approximately 50 percent [10].

Established but modifiable risk factors for obesity, cardiovascular disease and diabetes include physical inactivity, excessive energy intake and consumption of animal fats, including trans fatty acids. During the past four decades, Qatar has gone through a revolution in its socio-economic status, which has led to changes in their food habits, consumption patterns, lifestyles, and health status [9,11-13]. The healthy traditional food habits, characterized mainly by the consumption of vegetables, fruits, milk and beans, shifted to a western-like food habits characterized by higher intake of meat, trans fats, and carbohydrates, coupled with lower intake of vegetables and fruit, which are the main risk factors for obesity [14-16]. The sedentary lifestyle together with an obesity-promoting diet has led to the marked increase in levels of overweight and obesity among Qatari [13]. This change in dietary pattern and lifestyle among Qatari population is associated with increased prevalence of diet-related chronic diseases such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), hypertension, obesity, cancer, and osteoporosis [17-21].

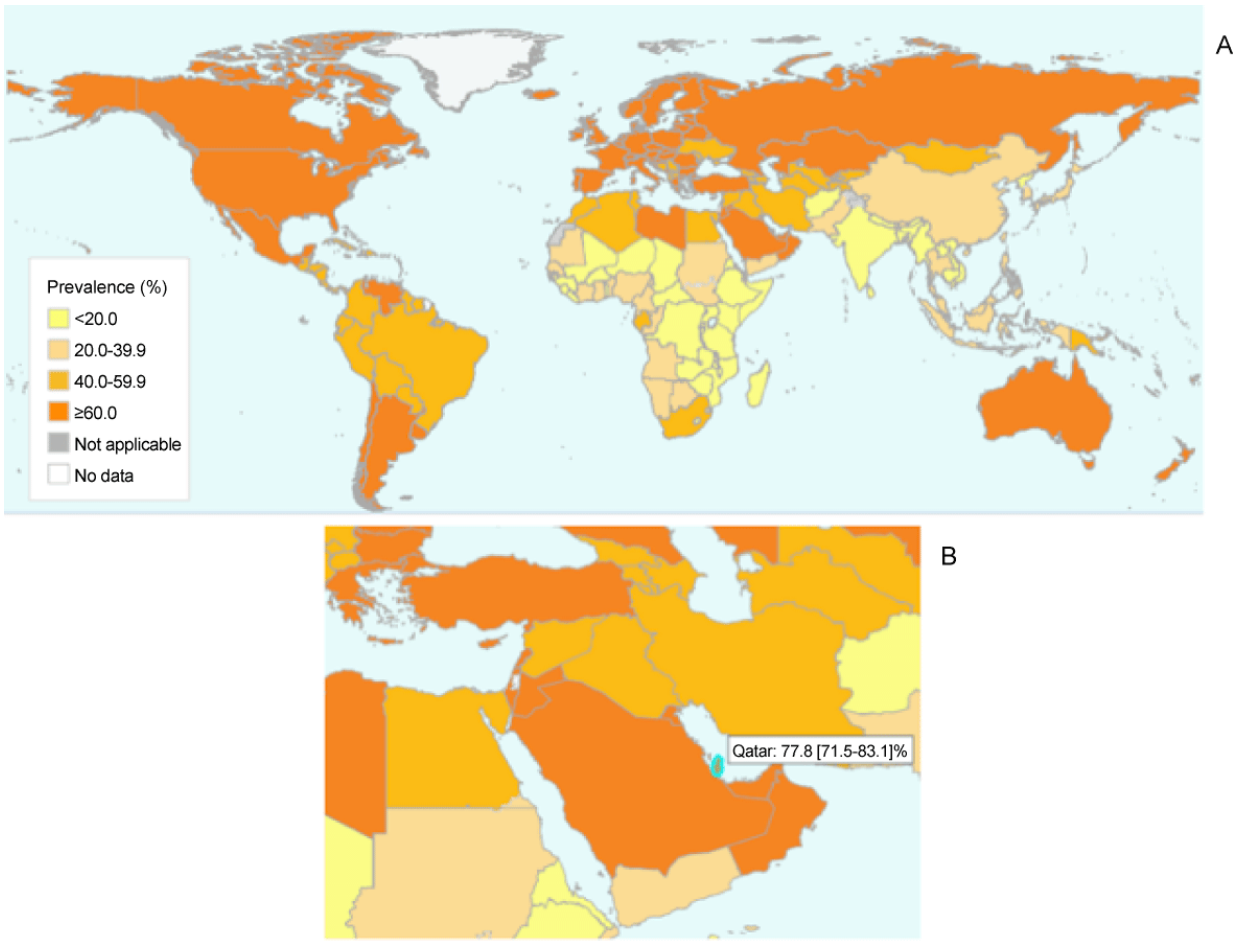

Figure 1: Prevalence of overweight worldwide (Figure 1A) and Middle East (Figure 1B) from 2014 WHO country profile (Reprinted from "Prevalence of overweight, age 18+, 2010-2014 (age standardized estimate). Both sex. 2014", **http://gamapserver.who.int/gho/interactive_charts/ncd/risk_factors/overweight/atlas.html**, Copyright WHO 2015).

The data about obesity are alarming, with more than 70% of the adult population overweight or obese [4]. The young population is extremely affected, as well. A cross sectional study of 1213 Qatari children (683 girls and 530 boys) aged 9-11 years old showed that the prevalence of overweight and obesity affected 21.1% and 17.7%, respectively [22]. In another study, Bener and Kamal [23] reported that the overall prevalence of overweight and obesity among children and adolescents was 19.8% and 4.3%, respectively [23]. The prevalence of overweight and obesity increased with age with a maximum rate was observed among boys compared to girls. The same pattern was observed among adolescents. Results of a study conducted among a representative sample of 1167 secondary school children (526 boys and 641 girls) aged 14-20 years old, showed that 21.4% of adolescents were overweight and 20.7% were obese [24].

Genetic determinants of obesity: the peculiar case of Qatar

A paper published in Nature Genetics in the 2009 identified 17 new loci associated with BMI [25] resulted from a genome wide association study (GWAS). These loci were linked to appetite control, neuronal control, growth and development, intracellular lipid transport, adipocyte metabolism, and cellular apoptosis. The Database Online Mendelian Inheritance in Man (OMIM) identifies more than 500 gene variants associated to the obesity [26]. Although GWAS studies

identified a rich source of candidate genes, which permit a personalized nutritional approach to obesity, they not yet defined the genetic pathway that underlies obesity onset in the general population [27,28]. Additionally, it has to be noted that most of these studies have mainly been focused on Western populations and their findings do not necessarily apply to populations of a different genetic background. A recent study interestingly showed that the genetic risk for T2DM decreased as humans migrated toward East Asia, highlighting a genetic risk differentiation across human populations [29].

In Qatar and other Middle East countries, local studies are lacking. Clearly, additional research is warranted to clarify possible specific genetic determinants in population disproportionately affected by obesity and NCDs, like the Qatari and Middle Eastern populations. The Qatari population is characterized by a very small size and a peculiar genetic background that defines three genetic groups according to their migration history (Bedouin, Persian-South Asian, and African tribes) [30]. Moreover the practice of first-cousin marriages has resulted in high level of inbreeding, with a consanguinity rate that can reach 54% [31]; noteworthy, more than 70% of the adult population is overweight or obese [4]. A recent study from Mezzavilla and colleagues [32] has pointed carbohydrate metabolism as one of the functional pathways identified by homozygosity mapping in the Qatari population. Additionally, two studies started to explore possible candidate genes for obesity in Qatari subjects: the first identified an association of PPARγ variant with obesity and hypertension [33]. The second one has tested the relevance of 23 loci found associated to obesity in previous studies in the Qatari population. The SNPs were chosen as mapping within or nearby well-documented obesity genes (including FTO and MC4R) and as representative of the obesity status (both in terms of BMI and waist circumference) [34]. Interestingly, only two of the 23 SNPs were found to be associated to obesity in the Qatari population, suggesting the existence of additional loci whose number and effect size still remain unknown. A more intense effort should be put in the identification of obesity loci specific for the Qatari population.

Although genetic factors can determine the propensity of an individual to develop obesity, the recent increase in obesity probably reflects environmental and lifestyle changes where dietary change is a major contributor and could interact with the genetic background [35].

Nutrigenomic approaches to obesity

Nutritional genomics refers to sciences that study the interactions between dietary components and the genome as well as resulting changes in gene expression, proteins and metabolite activities. Transcriptome, methylome, metabolome, and microbiome composition are the arguments pointed by nutrigenomics and metabolomics. Recently, advanced technologies (as next generation sequencing, high-density micro-arrays, mass spectrometry, and bioinformatics) allowed us to easily approach these sciences [36]. Great interest is growing around the opportunities from the personalized nutrition and its application to the complex diseases, as obesity. Several studies reported significant results in nutrigenomics, but we are far from the complete list of food-gene interactions [37,38]. Some successful examples are in cancers: for example, Lee and colleagues demonstrated that β-carotene consumption is protective against breast cancer in subjects with the diplotype TG: TG at codons 786-894 of NOS3 gene, on the contrary vitamin E is protective in TC or TT individuals for NOS3 codon 786, and in GT or TT for NOS3 codon 894 [39]. Fatty fish consumption was inversely associated with risk of prostate cancer in Swedish men carrying the variant rs5275 at gene COX2 [40]. Naturally, also obesity studies identified potentially genetic targets interacting with specific nutrients [41], for example a study from Mattei et al. [42] demonstrated that dietary fat intake interacts with TCF7L2 rs7903146, changing BMI, total fat mass and trunk fat mass [42]; another study from Zhang et al. [43] found that high-protein diet interacts with FTO rs15558902, improving weight loss, body composition and body fat distribution [43]. Other examples come from literature particularly from Europe and America, while the situation is different in Middle East, where the nutrigenomic approach to obesity and NCDs is still starting first attempts. Fahed et al. [15] 3 years ago, asked a call for nutritional genomics research in Arabic countries from North Africa to the Middle East [15]. In the meantime, only few studies were completed: the first study measured the metabolic perturbations in T2DM patients in Qatar; another one evaluated the DNA methylation in T2DM Palestinian patients; the last evaluated the smoking effect on DNA methylation in Qatari subjects [44-46].

Under the definitions of epigenetics we can insert the classical DNA methylation and histone acetylation mechanisms, as well as miRNA transcriptional control. It's well established that epigenetic mechanisms are involved in obesity, creating the "cycle of obesity" among the generations [47]. Both maternal and paternal diet influences obesity susceptibility in the offspring [48]. On the other hand, maintaining the appropriate metabolite level depends on gene regulation operated by specific miRNAs in target tissues, like adipose tissue, pancreas, liver, etc. [49]. The only Qatari study on epigenetics investigated possible epigenetic effects of smoking. The authors confirmed other population data, finding higher smoking impact in women, particularly in two proteins AHRR and PAR4, involved in cell growth and differentiation and platelet activation, respectively [45]. Another study in Arab population is from Toper off and colleagues, who identified an inverse correlation between leukocyte methylation status and T2DM, independent of sex and BMI, but increased by age [46].

Recent whole-genome transcriptome studies demonstrated different gene pathways activation in obese subjects. Lee et al. [50] investigated a time-course change in gene expression in mice during 24 weeks high fat diet, and identified differential expressed gene in oxidative phosphorylation, lipid metabolism and cell cycle pathways. The authors also investigated the differences in brown adipose tissue (BAT) genes respect to white adipose tissue (WAT), reporting increased levels of leptin and adiponectin in BAT and a consequent differential immune response [50]. A similar study measured the gene expression changes in mice WAT and liver tissues after long-term high fat diet, and confirmed a transcriptome transition in the 24 analyzed weeks, that evolved in the perturbation of lipid metabolism and immune system homeostasis [51]. The only human study is conducted on 1200 multiethnic subjects, and more the 10.000 gene levels were measured in purified monocytes. The authors demonstrated that the most significant pathway associated to BMI was cholesterol metabolism. Moreover they discovered that this pathway correlated with the inflammatory markers IL-6 and CRP, and with increased risk to develop type 2 diabetes and coronary arterial calcifications [52]. No Qatari or Arabic transcriptome studies on obesity were identified in recent publications.

Microbiome and metabolomics

Gut microbiota is a dynamic structure, which evolves from the birth to adulthood, and several factors such as diet, genetic background, and

immune status affect its composition. Alterations in one or more of this mechanism may be the cause of microbiome shift in several chronic inflammation diseases, like inflammatory bowel diseases, obesity, diabetes, asthma, non-alcoholic fatty liver disease (NAFLD) [53,54]. Advances in technologies, like next generation sequencing (NGS), allowed evaluating the whole microbiota composition in different conditions. The composition of the microbiota can modulate, through different mechanisms, the efficiency of energy extraction from the diet [55], lipid metabolism and storage in the liver and adipose tissue, intestinal permeability, modulating secretion of enteroendocrine hormones, affecting bile acid metabolism and inducing metabolic endotoxemia and inflammation [56-58].

It is now recognized that the development of obesity is associated with alterations in the gut microbial composition and activity. Obese individuals have an altered gut microbiota compared to lean controls [56]. Analysis of the gut microbiome and metabolic functions in obese and lean mice revealed an enrichment of genes involved in energy harvest, including genes involved in sensing and degrading dietary mono- and polysaccharides [59,60], in small chain fatty acids (SCFAs) metabolism [61], and amino acid metabolism, generating bioactive metabolites, as histamine and γ-amino butyric acid (GABA), which have immune-regulatory and anti-inflammatory functions [57]. Both intestinal and systemic inflammation, associated to different microbiota pattern, was observed in obese subjects vs not obese subjects, due to dendritic cell activation [62], and to the increased intestinal permeability. Several immune cell receptors, like Toll-like receptors (TLRs), have been shown to be activated by lipopolysaccharides (LPS), bacterial DNA, and peptidoglycan derived from the gut microbiota, leading to cytokine production and inhibition of insulin signaling through NF-kB or MAPK pathways [63]. The gut microbiota thus directly contributes to obesity by increasing energy harvest and nutrient metabolism from the diet, and activating inflammatory response.

Altered dietary intake has a major impact on gut microbial composition [64], and this can promote obesity and increase the risk of developing NCDs. Both its cellular composition and gene transcription network are rapidly altered in response to dietary shifts [56,65,66]. Dietary modification and probiotics / prebiotics supplementation are suggested as possible therapeutic approach to obesity, diabetes and other metabolic diseases, which involve microbiome changes [67-69].

Single countries or population studies well demonstrated that microbiome is influenced by environment and genetics, and changes across among populations [64,70,71], and the current knowledge about microbiome comes mostly from European and American studies. No data are available about microbiome composition in Qatari population, and moreover no study correlated microbiome with obesity in this population. We expect to find peculiar microbiome pattern in this population that could explain the higher incidence of obesity and CVDs [12].

Few studies were published on microbiome and human diseases in Middle East. A paper from Qatar University described possible microbiome investigation with germ-free animal models, and one study was already published on male fertility and microbiome role using this model [72,73]. The only human study is from Alokail and colleagues, which described the protocol to investigate probiotic effects in Saudi T2DM patients. The study is in progress and hopefully, it will provide evidences of benefic effects in diabetic patients, modulating microbiota and reducing inflammatory response [74].

Microbial activity is evaluated also measuring bacterial and human produced metabolites. Diet can modulate metabolite phenotype, and targeted analyses are performed to evaluate the effect of specific diets on metabolic disorders [75]. Several metabolomics studies have already been performed in the field of obesity and T2DM [76,77]. Metabolites from lipids, amino acids, and carbohydrates pathways are associated with BMI [78]. Mostly intercellular lipid intermediates, sphingolipids and bile acid intermediates are associated to obesity [77]. Microbial metabolism produces SCFAs from host amino acids, and changes in plasma levels of some amino acids are associated with T2DM [79], particularly aromatic amino acids. In a Qatari study, predictors of T2DM were identified in different body fluids, saliva, plasma, and urine, at different timescales of glycemic control, revealing a connection between metabolites across the body fluids and a specific association of metabolites with the timescales of glycemic control [44].

Future perspectives in Qatar

The nutrigenomic tools show a great potentiality for Qatar development and to improve health care system. The current studies about obesity in Qatar are mainly focused on epidemiology [6,20,21,80,81], genetics [33,34], cellular studies [82], and metabolomics [44]. No data are available about nutrigenomics, epigenetics, and transcriptome and microbiome analysis.

Qatar is making great efforts to develop research and education in the country [83,84]. Qatar government proposed a development plan, the Qatar National Vision 2030, based on four pillars: economic, social, human and environmental development [85]. The human development pillar is focused on build an educated and healthy population, and a capable and motivated workforce. Qatar Foundation (QF), a national non-profit organization for education, science and community development, considers research as essential to national and regional growth. Obesity, diabetes and cardiovascular diseases are among the key challenges asked by QF and the Qatar National Research Fund (QNRF) to be addressed by research community [86]. A great effort of Qatar research institutions are working to develop the translational research and to achieve the QNRF challenges, as Sidra Medical and Research Center, Weill Cornell Medical College in Qatar, Qatar Biomedical Research Institute, under the umbrella of QF, and other national institutes as Hamad Medical Corporation, Primary Health Care Corporation, and Qatar University. The newest technologies and expertise in genomics, bioinformatics and statistics are available inside the most of these institutions, which will potentially support any type of nutrigenomic study. These assumptions will promise the high-level outcomes from translational research and particularly from nutrigenomics in Qatar.

Conclusions

Qatar asks to address the determinants and the therapeutic approaches to chronic diseases, among which obesity shows a great urgency because of the high prevalence in the country. The nutrigenomics science will permit to assign a personalized nutritional intervention for NCDs. Great research efforts are focused to reach high levels of health care in Qatar.

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determinants of obesity; **KA**, **ET** and **AP** wrote the paragraph about obesity in Qatar; **CL** and **WE** contributed to the paragraph about genetic determinants of obesity, and reviewed the entire paper. **TA** wrote the paragraph about microbiome and metabolomics, reviewed the entire paper and coordinated the team.

Potential Conflict of Interest

Authors declare no conflict of interest.

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