IJBPAS, December, Special Issue, 2021, 10(12): 524-541

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON GENETIC VARIATION ASSOCIATED WITH METABOLIC SYNDROME AMONG THE SAUDI POPULATION

RANA ABDULLAH ALGHAMDI

Department of Chemistry, Science and Arts College, Rabigh Campus, King Abdulaziz University, Jeddah, Saudi Arabia

***Corresponding Author: Rana Abdullah Alghamdi: E Mail: raalghamdi3@kau.edu.sa**

Received 19th Aug. 2021; Revised 20th Sept. 2021; Accepted 29th Oct. 2021; Available online 1st Dec. 2021

https://doi.org/10.31032/IJBPAS/2021/10.12.2047

ABSTRACT

Genetic variation is a term used to explain the DNA disparity between individuals or the variations between populations. Various genetic variations have been reported across the Saudi population. While the origin of these variations is attributed to genetic factors, environmental factors also play a significant role in the phenotypical expression of the symptoms in MetS. The genetic factors can be attributed to natural selection due to the transfer of initially beneficial traits from ancestral generations to the present-day generations. Consanguinity marriages and inbreeding play a critical role in the genetic inheritance of traits that increase the risk of MetS. High frequency alleles are found in the incidence of type 2 diabetes, dyslipidaemia, hypertension and obesity—all of which contribute largely to the incidence and prevalence of MetS. This syndrom is more prevalent among females than males due to increased levels of inactivity in the former population.

Keywords: Genetic Variation, Metabolic Syndrome, Saudi Population, Type-2 diabetes

INTRODUCTION

Oil discovery in Arabian countries like Saudi Arabia increased the level of wealth, marking the beginning of dramatic changes in the nutritional requirements of the citizens. For instance, there were significant socioeconomic transitions from consuming locally grown natural foods to westernised fast foods and from conventional nomadic

lifestyles to urbanised sedentary living modalities. Such drastic changes in lifestyle have increased the prevalence of nutritional disorders—diabetes, obesity and metabolic syndrome (MetS). These abnormalities become more prevalent as the population continually becomes obese.

The discovery of MetS can be traced back to 1923 and is associated with the scientific work of Kyln, who described the disorder as a combination of high blood pressure, high blood sugar and gout[1]. Ever since, MetS has been associated with many other abnormalities, including microalbuminuria, fibrinolysis, coagulation, glucose intolerance, high levels of triglycerides, and decreased blood levels of high-density lipoproteins (HDL)[2]. The syndrome plays a critical role as a predisposing factor in the incidence of cardiovascular diseases and type 2 diabetes, explaining its scientific significance in pathology [3].

MetS is a universal concern, affecting between 20% and 25% of the global population with a significant increase over time[4]. The continuous increase in these statistics is linked to the progressive Westernisation of lifestyles characterised by little or no physical activity and high levels of obesity[2]. A wide sample population study conducted between 1995 and 2000 reported a 40% prevalence rate of MetS among adults in the Kingdom of Saudi Arabia (KSA)[5]. Various other studies have confirmed the significantly high prevalence rates of MetS in the recent past. However, there are significant variations among populations, ranging between 8% and 43% in men and from 7% to 56% among women[6]. Other than lifestyle, the prevalence of MetS is influenced by other essential factors like genetics, socioeconomic status and diet[7]. The differences in the prevalence rates are based on the population characteristics, including ethnicity, age and sex, geographical locations and the specific criteria applied in defining MetS [8]. This study explores the role of genetics in presenting the essential manifestations of MetS in the Saudi population.

MetS Risk Factors

Various factors predispose an individual to MetS, whether the individual's origin is Saudi Arabia or any other part of the world. For instance, research has noted a significant increase in the prevalence of MetS with an increase in age. The disease has a 10% prevalence among people aged below 20 years and a 40% prevalence among populations aged 60 and above[5,9]. However, a study

indicated that one in every eight school-going children manifests with three or more components of the disease [10]. Regarding racial disparities, the disease is more common among Hispanics and Asians than other races [11,12]. Progressive weight gain further affects the incidence rates of MetS, considering that only 5% of people with a normal weight may suffer from the disease compared to a prevalence of 22% among overweight people. Furthermore, the prevalence rate of MetS may increase to 60% in obese persons [13,14]. Abdominal obesity increases the risk of suffering from MetS more than normal obesity[15].

MetS is higher among people with a family history of type 2 diabetes or gestational diabetes[15]. Other diseases predisposing people to MetS include cardiovascular disorders, hypertension and polycystic ovary syndrome[16–19]. Polycystic ovary syndrome resembles MetS, affecting female reproductive hormones and has been associated with higher risks of developing MetS among women[18]. Research has further established that physical activity involving a 30-minute exercise programme for five days a week without any medical contraindication played a critical role in reducing the incidence of MetS[20]. It should be noted that exercise positively impacts blood cholesterol levels, blood pressure and insulin sensitivity, thereby reducing the risks of developing complications that could predispose anyone to MetS. These impacts prevail even without significant weight loss[20]. The Mediterranean diet conventionally used in Greece, Southern France, Crete and some parts of Italy has shown a significant improvement in MetS prevention[9]. The diet contains olive oil and reasonable quantities of carbohydrates and proteins, including fish and chicken; combining these food items with fruits and vegetables, nuts and grains improves the overall health and reduces the risk of developing MetS[21]. Smoking and alcoholism also increase the risk of developing the disease[22], although genetic factors play a major role in influencing the disease etiology[23].

Genetics of MetS

The genetics of MetS can be further linked to a history of type 2 diabetes mellitus and insulin resistance, which have been discussed as two predisposing factors for MetS. While a family history of obesity is further linked to higher chances of developing the disease, specific genetic loci play a pivotal role in disease causation and exacerbation due to their linkage disequilibrium with MetS[24]. For instance, a genome-wide scan using a 10-

cM map demonstrated a quantitative trait locus on chromosome 3q27 that was strongly associated with weight, waist and hip circumferences, insulin and leptin [25]. In another quantitative trait locus on chromosome 17p12, a strong linkage with plasma leptin levels was reported[26].

In a study among patients with related diseases, such as coronary artery disease, there was a strong association between the incidence of the condition and genetic factors. It should be remembered that coronary artery disease is one of the predisposing factors for MetS. In the study, it was noted that the existence of single-nucleotide polymorphisms is associated with MetS in the participating population[27]. However, some genes showed an association with males more than females in the incidence and exacerbation of MetS. The specific genes associated with MetS include the COL5A2, SELE, LIPC, IL6, TGFB, IL1R1 and LDLR gene[27]. It was also found that there was a high frequency of val162 alleles of the leu162-to-val polymorphism expressed in the PPARA gene among research participants with abdominal obesity and hypertriglyceridemia, both of which are strongly associated with MetS, these findings were also observed in animal models, indicating a strong correlation between MetS and genetic variations [28].

Pathophysiology

The pathogenesis of MetS is commonly associated with insulin resistance, explaining why the disease is sometimes referred to as insulin resistance syndrome. This syndrome is characterised by high levels of insulin in the blood due to defective insulin action necessary for maintaining euglycemia. The greatest contributing factor to insulin resistance is excessive circulation of fatty acids resulting from enlarged adipose tissue masses[29]. The fatty acids play a critical role in blocking insulin receptors, thereby inhibiting insulin-mediated glucose uptake. When the fatty acids circulate to the liver, they facilitate an increased secretion of glucose, triglycerides and very low density lipoproteins (VLDL). Consequently, there is little or no transformation of glucose into glycogen for storage and an increase in the levels of accumulated triglycerides[2]. A combination of these factors predisposes an individual to abdominal obesity—a crucial factor in MetS development [30]. However, it is important to note that people with normal weights could also suffer from insulin resistance in what is referred to as metabolic obesity in normal weight individuals.

The pathogenesis of MetS is further associated with dyslipidaemia characterised by a high secretion of VLDLs in the liver. Under normal physiology, insulin plays a critical role in reducing the tendency of VLDLs to flow into the systemic circulation[31]. However, insulin resistance increases the influx of free fatty acids into the hepatic system, thereby increasing triglyceride synthesis[32,33]. As such, detecting hypertriglyceridemia has acted as a key indicator in MetS diagnosis[34]. Research has also noted a significant decrease in the level of high density lipoproteins (HDLs) cholesterol in the aetiology of MetS due to alterations in the composition and metabolism of HDL amidst insulin resistance[35]. Hypertriglyceridemia decreases the blood levels of HDL cholesterol content due to a decrease in the cholesteryl ester component of the lipoprotein core. Notably, the modifications in LDL composition occur similarly.

These activities eventually induce glucose intolerance due to a characteristic failure of insulin action to suppress gluconeogenesis in the hepatic system. A similar result is the inability of insulin action to mediate glucose uptake from highly sensitive tissues, including the muscles and the adipose tissue[36]. Insulin resistance is also associated with high blood pressure, considering that insulin is a vasodilator, especially when administered to patients with a normal weight, but eliciting secondary impacts on renal sodium reabsorption. As such, these conditions contribute to a series of events that induce MetS[37]. The susceptibility factors described here contribute to the genetic variations of MetS in Saudi Arabia.

Genetic Variations in the Kingdom of Saudi Arabia

Combining the abovementioned factors contributes to an increased probability of suffering from cardiovascular atherosclerotic disease, thereby inducing MetS development. In any case, the International Diabetes Federation reported that about a quarter of the global population suffer from MetS. In a literature review conducted to investigate the prevalence of MetS in Saudi Arabia, the authors reported a variance between 13.6% and 57%[38]. The variation could be explained by the existing differences in gender, age groups, and the criteria used to define MetS. However, it is noticeable that females suffer more from the disease than their male counterparts—a variation also associated with an increase in age. For instance, a large cross-sectional survey reported a prevalence of 39.3% of MetS

among women aged between 30 and 70 years in the country[27]. While genetics play a critical role in these variations, the environmental factors surrounding the population cannot be underestimated, particularly because the phenotype influences genotypical outcomes in population characteristics.

Environmental Factors Influencing Genetic Variations

Environmental factors contributing to high prevalence rates of MetS in the Kingdom of Saudi Arabia include an increased consumption of foods high in fat, carbohydrates and salts. Further, the disease prevalence may be markedly high in cases where the consumption of fruits and vegetables is reduced and exacerbated by low levels of physical activity. Various investigations conducted in the Kingdom have revealed the role of diet and physical activity in influencing the genetic variations existing in the aetiology and exacerbation of MetS. A recent example can be noted from the findings of the Saudi Interview Survey, which was conducted to measure health indicators across 13 administrative regions in the Kingdom. The survey followed the lifestyles of 10,735 participants aged 15 to 65. The findings of the survey indicated that only 6.7% of the surveyed population served above five servings of fruit and vegetables daily[39]. In another survey conducted among military personnel involving 10,500 participants, it was reported that a significantly large population (87.6%) continued to rely on fast foods weekly, compared to 44.8% of the population that reported serving fruits and 32.6% who reported a weekly consumption of vegetables[39]. Similar studies investigating the lifestyles of adolescents reported related findings, with an increasing trend in the consumption of calories and fat. While many investigations have associated eating habits with a significant predisposition to MetS, the consumption of salt has not been widely studied to establish its role in the increasing prevalence rates of the syndrome. For instance, only a limited study involving 87 participants was found to be significant under this review, which indicated that the daily consumption of salt among the targeted population exceeded the recommended quantities[39]. Furthermore, it is highly likely that the frequent consumption of fast foods may contribute to high salt intake, considering the association of fast foods with a high intake of salt. These factors are worsened by significant physical inactivity among the Saudi population.

Research has established that the levels of physical inactivity among Saudi Arabian adolescents exceed those among similar populations in other parts of the world; for instance, a cross-cultural review comparing the level of physical inactivity between adolescents from the United Kingdom and the Kingdom of Saudi Arabia revealed that the latter population was largely inactive[40]. In the same study, the proportion of individuals engaging in physical activities was higher in the UK than in Saudi Arabia. The comparative study indicated the prevailing role of attitude in physical activity, with females showing a lesser interest in participating in physical exercises[41]. The situation gets a lot worse, considering that some physical activities are never practiced by women at all. Consequently, females are more likely to live sedentary lifestyles than males in the Kingdom of Saudi Arabia. The case is also similar in adolescents, where more girls are associated with sedentary lifestyles than boys. The poor attitude of females and girls regarding physical exercise could be a cultural factor in Saudi Arabia due to the limited support given to women towards physical exercise [42]. Apparently, the exposure of the Saudi population to fast foods, limited consumption of fruits and vegetables and increased levels of physical inactivity contribute significantly to the high prevalence of MetS[43]. Since the level of physical inactivity is higher in females than in males, it explains the higher prevalence rates of the disease among females compared to men.

The genetic variations associated with MetS among the Saudi population are linked to various determinants that also increase the risks of elevating an individual's blood sugar, pressure, dyslipidaemia and obesity. Genome-wide studies investigated these risk factors and found a correlation between the disease and various components affecting fat metabolism, glucose detection, appetite control, and insulin signalling. In a study involving 285 candidates resenting MetS symptoms, genetic variants related to the vitamin D receptor gene were found to be directly linked to the regulation of fat metabolism[32]. As such, these variants influence the incidence rates of MetS among the target population. However, such studies fail to link the genes in proximity to the vitamin D gene with the increasing incidence rates of MetS in Saudi Arabia.

Further, the genetic components associated with MetS are closely related to those linked to the causation and exacerbation of diabetes. According to the literature, about 60 loci are directly linked to the development

and progression of type 2 diabetes mellitus in European and Asian populations. This genetic variation suggests the possibility that different genes in proximity at the genome level participate in the development of diabetes. Nonetheless, studies have established that the 60 loci could only be associated with about 10% of the total diabetes heritability[44]. Up to 50 single nucleotide polymorphisms associated with higher risks of diabetes have been investigated in the Kingdom of Saudi Arabia, although only 12 out of these polymorphisms were directly linked to diabetes risk factors[45]. Nonetheless, replication of the study findings was limited, probably explained by the relatively small sample sizes included in the studies. Other than the vitamin D receptor gene, which expresses protective responses to the development of diabetic symptoms, the rest of the genes in the loci indicate higher risks of developing the disease, further predisposing patients to MetS[5]. The expression of such genes influences insulin secretion by interfering with beta cell maturation and the insulin signaling process. Other relevant genetic variants influence the modulation of insulin action in pancreatic beta cells, raising the risk of MetS in the Saudi population [45].

Concurrently, genetic variations contributing to hypertension in the target population further increase the risk of developing MetS in the Saudi population. Nevertheless, the number of genetic variants associated with increased risks of hypertension (and therefore MetS) is lesser compared to the previously discussed variations in diabetes mellitus. For instance, studies conducted so far only associate 32 single nucleotide polymorphisms associated with hypertension in the population compared to the 50 polymorphisms associated with the former risk factor for MetS. However, investigations revolving around hypertension have been less successful compared to prior studies involving other chronic diseases. Once again, small sample sizes in genome-wide studies conducted to investigate the role of genetic variation in hypertension affect the generalisation and replication of the findings.

Among the Saudi population, genetic variations associated with the incidence of MetS were found to be closely linked to the loci of genes affecting blood pressure through different mechanisms. For instance, an increase in blood pressure was documented in Saudi populations with homozygous mutations affecting the methylenetetrahydrofolate reductase gene. The

aforementioned gene is associated with an increase in the levels of homocysteine and increased blood pressure associated with elevated arteriolar constriction and a subsequent increase in the reabsorption rates of sodium[46]. The angiotensin converting enzyme gene operates similarly, increasing blood pressure through vasoconstrictive effects. Another gene involved in blood pressure regulation is the cytochrome P450 gene, which increases the risk of high blood pressure by modulating sodium transportation in the kidneys. Genes increasing risks of hypertension further increase the chances of suffering from MetS, explaining the genetic variations among the Saudi population [47].

The genetic components of obesity have also been largely associated with a high risk of suffering from MetS among the Saudi population. However, investigating the genetic factors associated with obesity is more complicated than investigating the genetics of hypertension and diabetes. It should also be remembered that obesity is a risk factor for diabetes, considering the similar genetic components in the two conditions[9] In different studies conducted across the Saudi population, up to 48 single-nucleotide polymorphisms associated with obesity have been documented. For instance, the frequency of the Arg16Gly polymorphism of the β2-adrenergic receptor gene in Saudi populations involved in genome-wide studies was higher in obese and overweight participants compared to lean controls[48]. While the genotype effects in such studies indicate an increase in the incidence rates of obesity, the allelic effects are associated with obesity protective effects[36]. However, many studies tend to increase the involvement of participants with diabetes and obesity as comorbidities when studying the genetic components of obesity, a situation considered to increase the risk of bias. Bias occurs because the high likelihood of factors affecting diabetic patients also affects obese patients due to the associated possibilities of lifestyle modifications and the impacts of diabetes medications. While the clathrin-associated adaptor complex was associated with the regulation of intracellular vesicle transportation, the gene was only common in other Asian countries, but uncommon among the Saudi population [49].

Other genes, such as the brain-derived neurotrophic factor and the fat mass and obesity associated genes, have also been linked to changes in eating patterns, significantly impacting the incidence rates of obesity among Saudi Arabians[50]. The fat mass

and obesity-associated genes along with their variants are also linked with diabetes traits, explaining the close linkage between the development and progression of diabetes, obesity and MetS[45]. Variants in proximity with the fat mass and obesity-associated genes also play a critical role in increasing the risks of diabetes and MetS among Saudi Arabians[51]. Nonetheless, the impact of such genes on type 2 diabetes mellitus has been postulated to be associated with the consequences of an individual's body mass index.

Genetic variations in the target population further revolve around the genetic factors influencing the incidence of dyslipidaemia. For instance, the polymorphisms associated with the HDL cholesterol, triglycerides and LDL cholesterol levels with about 13 genetic loci involved in regulating lipid metabolism have so far been detected[52]. The polymorphisms associated with the regulation of lipid metabolism in Saudi populations are also linked to an increased risk of developing type 2 diabetes mellitus, leading to a cascade of events that eventually induce MetS. In a study, the carriers of Arg16Gly polymorphism of the β2-adrenergic receptor gene were associated with high secretion levels of LDL and triglycerides, although HDL secretion was insignificant [45].

APOA1, APOA2, APOA5 and APOB are all apolipoprotein genes that regulate lipid metabolism and they were found to be significant genotypes for obesity traits that may influence MetS risk [53–56]. Liam and his colleagues reported that in patients with T2DM, apoB is substantially associated to MetS regardless of LDL-C level. Of the components of MetS, TG, and systolic blood pressure seemed to be predictors of apoB [57]

According to the Hardy–Weinberg law, the frequency of alleles is constant in circumstances where genomic traits are transferred through generations provided that mating occurs randomly across populations without selection, migration or mutation[58]. Unfortunately, the Saudi Arabian population faces historical factors that may have affected allelic frequencies, interfering with the initial Hardy–Weinberg equilibrium[59].

The Kingdom was established about 80 years ago and is characterised by deserts cutting across the geographical region. Traditionally, the country faced major challenges associated with lack of resources right from its inception, making it one of the poorest countries globally at that time. Considering these circumstances, the population could have undergone natural selection, eliminating the weak and retaining

those that could persevere the prevailing conditions. However, the situation changed greatly about 20 to 30 years ago after the discovery of one of the greatest oil sources in the eastern region of the country. The country witnessed a significant economic surge in the period, changing the lifestyles of the entire population. During this period, the population witnessed an increase in food supply, leading to a change in lifestyles to adopt Westernised ways of living. Consequently, many people in the country started suffering from obesity and overweight, conditions that can be explained by the thrifty genotype hypothesis [23].

Depending on the ability of certain people to survive under different prevailing conditions, natural selection significantly influences allelic frequencies. For instance, genotypes that are selected in the natural selection process experience an allelic frequency under the prevailing conditions [60]. In situations where an individual carries an unselected gene, a reduction in viability and fertility is witnessed, leading to reduced chances of such a genotype being transferred across generations. The thrifty genotype hypothesis has been used previously to explain variations in the incidence of obesity and type 2 diabetes among other populations in the past[45]. According to the theory, certain genotypes could be beneficial during starvation and environmental factors, such as limited food availability. Furthermore, natural selection could have enhanced the frequency and many favoured genotypes that could have increased the risk of metabolic disorders like obesity and diabetes[61]. While such genotypes could have been advantageous during starvation, their maintenance in periods of plenty potentiates increased the risk of MetS. According to a research done on female students at a Saudi university, an increasing number of young girls are being identified with MetS as a due to bad eating habits, with the lack of physical activity producing increased body weight and the probable advancement of chronic illnesses [53].

Inbreeding in Saudi Arabia has also been extensively discussed in the literature and can be used to explain the persistence of some of the genetic variations associated with MetS in the country. For instance, a study established that about 54% to 57% of the population engaged in consanguineous marital relationships, with a majority being associated with first-degree cousins[62]. The prevalence of such marriages is highest in the country's rural areas and depends on various social and traditional factors. It is notable that many families in the country strictly adhere to

cultural behaviours, with marriages between first-degree cousins being almost the norm in the Kingdom. In any case, natives argue that it is easy to mediate marriages between close relatives, enhancing the behaviour of bringing mating persons to a similar environment. In such arrangements, it is easy to initiate spousal adjustments postmarriage while enhancing the stability of such relationships. Additionally, other researchers have reported economic reasons for inbreeding, including the ability to retain wealth within the same family or tribe[62].

Despite the alleged benefits of inbreeding in Saudi Arabian society, various disadvantages have been enumerated, particularly regarding the increased prevalence of MetS in the country. For instance, this behaviour increases the aggregation of type 2 diabetes risk alleles, with many sources of literature proposing a persistent synergism between consanguineous marriages and type 2 diabetes[63]. The degree of inbreeding influences the inheritance of commonly shared ancestral alleles. If alleles responsible for the associated risk factors for MetS are inherited, the likelihood of such a disorder persisting in the population is significantly high. On many occasions, the shared allele is the genotype for type 2 diabetes, leading to high levels of heredity in the disease transmission. While the inherited alleles could be silent, environmental factors associated with MetS persist in the region, explaining why the genes could be expressed randomly across the entire population[45].

CONCLUSION

Saudi Arabia has one of the highest rates of Mets in the world. Despite the fact that the risk factors for Mets in Saudi society were identical to those identified worldwide. MetS is characterized as a cluster of interrelated biochemical, physiological, clinical, and metabolic variables that raise the risk of atherosclerotic cardiovascular disease, type 2 diabetes, and all-cause mortality. For this demographic, each individual component of Mets, as well as the illness itself, could be influenced by genetic factors. A family history of obesity, type 2 diabetes, and/or insulin resistance significantly increases the likelihood of developing Mets.

Conflict of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Source

No financial support was needed nor provided for this work.

Declaration

The author declare that this work is original and has not been submitted for publication elsewhere.

REFERENCES

[1] Kylin, E. Studien ueber das Hypertonie-Hyperglyka" mie-Hyperurika" miesyndrom. *Zentralblatt für Inn. Medizin* **44**, 105–127 (1923).

[2] Cornier, M. A. *et al.* The metabolic syndrome. *Endocrine Reviews* **29**, 777–822 (2008).

[3] Gimeno-Orna, J. A. *et al.* Microalbuminuria accounts for the increased vascular disease risk in diabetic patients with metabolic syndrome. *Rev. Española Cardiol. (English Ed.* **60**, 1202–1205 (2007).

[4] Ranasinghe, P., Mathangasinghe, Y., Jayawardena, R., Hills, A. P. & Misra, A. Prevalence and trends of metabolic syndrome among adults in the asia-pacific region: a systematic review. *BMC Public Health* **17**, 1–9 (2017).

[5] Al-Nozha, M. *et al.* Metabolic syndrome in Saudi Arabia. *Saudi Med. J.* **26**, 1918 (2005).

[6] Cameron, A. J., Shaw, J. E. & Zimmet, P. Z. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol. Metab. Clin. North Am.* **33**, 351–375 (2004).

[7] Tamashiro, K. L. K. Metabolic syndrome: links to social stress and socioeconomic status. *Ann. N. Y. Acad. Sci.* **1231**, 46–55 (2011).

[8] Gurka, M. J., Filipp, S. L. & DeBoer, M. D. Geographical variation in the prevalence of obesity, metabolic syndrome, and diabetes among US adults. *Nutr. Diabetes* **8**, 1–8 (2018).

[9] Alzahrani, A. M. *et al.* Prevalence and predictors of metabolic syndrome among healthy Saudi Adults. *Br. J. Diabetes Vasc. Dis.* **12**, 78–80 (2012).

[10] Andrabi, S. M. S. *et al.* Prevalence of metabolic syndrome in 8–18-year-old school-going children of Srinagar city of Kashmir India. *Indian J. Endocrinol. Metab.* **17**, 95 (2013).

[11] Lora, C. M. *et al.* Chronic kidney disease in United States Hispanics: a growing public health problem. *Ethn. Dis.* **19**, 466 (2009).

[12] Palaniappan, L. P., Wong, E. C., Shin, J. J., Fortmann, S. P. & Lauderdale, D. S. Asian Americans have greater prevalence of metabolic syndrome despite lower body mass index. *Int. J. Obes.* **35**, 393–400 (2011).

[13] Strasser, B. Physical activity in obesity and metabolic syndrome. *Ann. N. Y. Acad. Sci.* **1281**, 141 (2013).

[14] Grundy, S. M. Metabolic syndrome: a multiplex cardiovascular risk factor. *J. Clin. Endocrinol. Metab.* **92**, 399–404 (2007).

[15] Björntorp, P. Abdominal obesity and the metabolic syndrome. *Ann. Med.* **24**, 465–468 (1992).

[16] Aballay, L. R., Eynard, A. R., Díaz, M. del P., Navarro, A. & Muñoz, S. E. Overweight and obesity: a review of their relationship to metabolic syndrome, cardiovascular disease, and cancer in South America. *Nutr. Rev.* **71**, 168–179 (2013).

[17] Schillaci, G. *et al.* Prognostic value of the metabolic syndrome in essential hypertension. *J. Am. Coll. Cardiol.* **43**, 1817–1822 (2004).

[18] Ali, A. T. Polycystic ovary syndrome and metabolic syndrome. *Ces. Gynekol.* **80**, 279–289 (2015).

[19] Apridonidze, T., Essah, P. A., Iuorno, M. J. & Nestler, J. E. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **90**, 1929–1935 (2005).

[20] Ansarimoghaddam, A. *et al.* Prevalence of metabolic syndrome in Middle-East countries: Meta-analysis of cross-sectional studies. *Diabetes Metab. Syndr. Clin. Res. Rev.* **12**, 195–201 (2018).

[21] Kastorini, C.-M. *et al.* The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J. Am. Coll. Cardiol.* **57**, 1299–1313 (2011).

[22] Lee, W.-Y., Jung, C.-H., Park, J.-S., Rhee, E.-J. & Kim, S.-W. Effects of smoking, alcohol, exercise, education, and family history on the metabolic syndrome as defined by the ATP III. *Diabetes Res. Clin. Pract.* **67**, 70–77 (2005).

[23] Ziki, M. D. A. & Mani, A. Metabolic syndrome: Genetic insights into disease pathogenesis. *Current Opinion in Lipidology* **27**, 162–171 (2016).

[24] Barrimah, I. E., Mohaimeed, A. R., Midhat, F. & Al-Shobili, H. A. Prevalence of metabolic syndrome among qassim university personnel in Saudi Arabia. *Int. J. Health Sci.*

(Qassim). **3**, 133 (2009).

[25] Alkahtani, S., Elkilany, A. & Alhariri, M. Association between sedentary and physical activity patterns and risk factors of metabolic syndrome in Saudi men: a cross-sectional study. *BMC Public Health* **15**, 1234 (2015).

[26] Matsubara, M., Maruoka, S. & Katayose, S. Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. *Eur. J. Endocrinol.* **147**, 173–180 (2002).

[27] Al-Rubean, K. *et al.* Anthropometric cutoff values for predicting metabolic syndrome in a Saudi community: from the SAUDI-DM study. *Ann. Saudi Med.* **37**, 21–30 (2017).

[28] Youssef, S. M. *et al.* Interaction Effects of the Leu162Val PPARα and Pro12Ala PPARγ2 Gene Variants with Renal Function in Metabolic Syndrome Population. *PPAR Res.* **2013**, (2013).

[29] Akbar, D. Metabolic syndrome is common in Saudi type 2 diabetic patients. *Hypertension* **12**, 47–49 (2002).

[30] Fatani, S. H., Abdelbasit, N. A., Al-Amodi, H. S., Mukhtar, M. M. & Babakr, A. T. Testosterone, obesity, and waist circumference as determinants of metabolic syndrome in Saudi women. *Diabetes, Metab. Syndr. Obes. targets Ther.* **11**, 175 (2018).

[31] Eckel, R. H., Grundy, S. M. & Zimmet, P. Z. The metabolic syndrome. *Lancet* **365**, 1415–1428 (2005).

[32] Bahijri, S. M. & Al Raddadi, R. M. The importance of local criteria in the diagnosis of metabolic syndrome in Saudi Arabia. *Ther. Adv. Endocrinol. Metab.* **4**, 51–59 (2013).

[33] Bahijri, S. M., Al Raddadi, R. M., Jambi, H., Alaama, M.-N. A. & Ferns, G. The prevalence of metabolic syndrome in an apparently healthy, normotensive and non-diabetic population in Saudi Arabia by two definitions: implications for local practice. (2013).

[34] Li, Z., Deng, M. L., Tseng, C.-H. & Heber, D. Hypertriglyceridemia is a practical biomarker of metabolic syndrome in individuals with abdominal obesity. *Metab. Syndr. Relat. Disord.* **11**, 87–91 (2013).

[35] Al-Daghri, N. M., Al-Attas, O. S., Wani, K., Sabico, S. & Alokail, M. S. Serum uric acid to creatinine ratio and risk of metabolic syndrome in Saudi type 2 diabetic patients. *Sci. Rep.* **7**, 1–8 (2017).

[36] Al-Daghri, N. M. *et al.* Selected dietary nutrients and the prevalence of metabolic syndrome in adult males and females in Saudi Arabia: a pilot study. *Nutrients* **5**, 4587–4604 (2013).

[37] Brocato, J. *et al.* Particulate matter from Saudi Arabia induces genes involved in inflammation, metabolic syndrome and atherosclerosis. *J. Toxicol. Environ. Heal. Part A* **77**, 751–766 (2014).

[38] Aljohani, N. J. Metabolic syndrome: Risk factors among adults in Kingdom of Saudi Arabia. *J. Family Community Med.* **21**, 170 (2014).

[39] Al-Rubeaan, K. *et al.* Prevalence of metabolic syndrome in Saudi Arabia-a cross sectional study. *BMC Endocr. Disord.* **18**, 16 (2018).

[40] Brocato, J. *et al.* Association between sleeping hours and cardiometabolic risk factors for metabolic syndrome in a Saudi Arabian population. *BMJ Open* **5**, (2015).

[41] Al-Daghri, N. *et al.* Serum leptin is elevated in Saudi Arabian patients with metabolic syndrome and coronary artery disease. *Diabet. Med.* **20**, 832–837 (2003).

[42] Alaklabi, A. M. & Alsharairi, N. A. Current evidence on vitamin D deficiency and metabolic syndrome in obese children: what does the evidence from Saudi Arabia tell us? *Children* **5**, 11 (2018).

[43] Alosaimi, F. D. *et al.* Prevalence of metabolic syndrome and its components among patients with various psychiatric diagnoses and treatments: A cross-sectional study. *Gen. Hosp. Psychiatry* **45**, 62–69 (2017).

[44] Kaur, J. A comprehensive review on metabolic syndrome. *Cardiology Research and Practice* **2014**, (2014).

[45] Gosadi, I. M. Assessment of the environmental and genetic factors influencing prevalence of metabolic syndrome in Saudi Arabia. *Saudi Med. J.* **37**, 12 (2016).

[46] Al-Qahtani, D. A. & Imtiaz, M. L. Prevalence of metabolic syndrome in Saudi adult soldiers. *Saudi Med. J.*

26, 1360 (2005).

[47] Roman, R. J. P-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol. Rev.* **82**, 131–185 (2002).

[48] AlQuaiz, A. M. *et al.* Women Health in Saudi Arabia: A review of non-communicable diseases and their risk factors. *Pakistan Journal of Medical Sciences* (2014). doi:10.12669/pjms.302.4378

[49] Mabry, R. M., Reeves, M. M., Eakin, E. G. & Owen, N. Gender differences in prevalence of the metabolic syndrome in Gulf Cooperation Council Countries: a systematic review. *Diabet. Med.* **27**, 593–597 (2010).

[50] Thaker, V. V. GENETIC AND EPIGENETIC CAUSES OF OBESITY. *Adolesc. Med. State Art Rev.* **28**, 379–405 (2017).

[51] Al-Daghri, N. M. *et al.* Association of VDR-gene variants with factors related to the metabolic syndrome, type 2 diabetes and vitamin D deficiency. *Gene* **542**, 129–133 (2014).

[52] Boes, E., Coassin, S., Kollerits, B., Heid, I. M. & Kronenberg, F. Genetic-epidemiological evidence on genes associated with HDL cholesterol levels: a systematic in-depth review. *Exp. Gerontol.* **44**, 136–160 (2009).

[53] Alghamdi, R. A., Al-Zahrani, M. H., Balgoon, M. J. & Alkhattabi, N. A. Prevalence of ApoB100 rs693 gene polymorphism in metabolic syndrome among female students at King Abdulaziz University. *Saudi J. Biol. Sci.* **28**, 3249–3253 (2021).

[54] Sánchez-Moreno, C. *et al.* APOA5 Gene Variation Interacts with Dietary Fat Intake to Modulate Obesity and Circulating Triglycerides in a Mediterranean Population. *J. Nutr.* **141**, 380–385 (2011).

[55] Mattei, J., Demissie, S., Tucker, K. L. & Ordovas, J. M. The APOA1/C3/A4/A5 cluster and markers of allostatic load in the Boston Puerto Rican Health Study. *Nutr. Metab. Cardiovasc. Dis.* **21**, 862–870 (2011).

[56] Phillips, C. M. *et al.* Gene-nutrient interactions and gender may modulate the association between ApoA1 and ApoB gene polymorphisms and metabolic

syndrome risk. *Atherosclerosis* **214**, 408–414 (2011).

[57] Lim, Y. *et al.* Apolipoprotein B is related to metabolic syndrome independently of low density lipoprotein cholesterol in patients with type 2 diabetes. *Endocrinol. Metab.* **30**, 208–215 (2015).

[58] Edwards, A. W. F. Anectodal, historical and critical commentaries on genetics. *Genetics* **154**, 1419–1426 (2000).

[59] Al-Qahtani, D. A., Imtiaz, M. L., Saad, O. S. & Hussein, N. M. AComparison of the prevalence of metabolic syndrome in Saudi adult females using two definitions. *Metab. Syndr. Relat. Disord.* **4**, 204–214 (2006).

[60] Sliem, H. A., Ahmed, S., Nemr, N. & El-Sherif, I. Metabolic syndrome in the Middle East. *Indian J. Endocrinol. Metab.* **16**, 67 (2012).

[61] Practice, C. R. and. Retraction: A comprehensive review on metabolic syndrome (Cardiology Research and Practice (2014) 2014 (943162) DOI: 10.1155/2014/943162). *Cardiology Research and Practice* **2019**, (2019).

[62] Shamy, M. *et al.* Association between exposure to ambient air particulates and metabolic syndrome components in a Saudi Arabian population. *Int. J. Environ. Res. Public Health* **15**, 27 (2018).

[63] Gosadi, I. M., Goyder, E. C. & Teare, M. D. Investigating the potential effect of consanguinity on type 2 diabetes susceptibility in a Saudi population. *Hum. Hered.* **77**, 197–206 (2014).