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The Risk of Genetic Variants and Socioeconomic Lifestyle for Insulin Resistance Traits: A Mini-review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Insulin resistance is a complex metabolic characteristic that increases the risk of developing cardiovascular disease which results from hypertension and dyslipidemia. The interaction of hereditary and environmental are factors driving the emergence of such disorders. Molecular techniques have now enabled the discovery of uncommon variations linked to the etiology of these disorders. Lipid metabolism is connected to various genetic variations associated with the etiology of metabolic syndrome. There are several genetic variants including epigenetic modifications alongside immunological status interference with pathogenic infectious that are directly related to insulin resistance and glucose metabolism. However, functional studies are required to determine the role of various genetic variations and other distinct factors in the development of insulin resistance. This review aims to give a broad overview of the interference of these genetic variants in the occurrence of insulin resistance. We also provide a summary of current developments in the environmental and immune factors associated with type 2 diabetes.

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1. INTRODUCTION

Insulin resistance (IR) is defined as an altered physiological response of target tissues, including the liver, muscle, and fat, to insulin stimulation. Hyperinsulinemia and increased synthesis of beta-cell insulin are the results of decreased glucose removal due to insulin resistance [1]. Insulin resistance is usually an acquired disorder caused by excess body fat, while genetic factors have been identified as well. As a widely recognized insulin resistance test does not exist, the clinical definition of insulin resistance remains unclear [2]. Contrarily, insulin resistance and compensatory hyperinsulinemia raise the risk of hypertension and dyslipidemia, as shown by elevated plasma triglyceride (TG) and decreased high-density lipoprotein cholesterol (HDL-C) levels. These amendments increase the risk of cardiovascular disease. Insulin resistance and compensatory hyperinsulinemia have become linked to several other clinical conditions. Polycystic ovary syndrome, for instance, appears to be due to insulin resistance and compensatory hyperinsulinemia. According to research, insulin resistance/hyperinsulinemia is more common in patients with nonalcoholic fatty liver disease, and some types of cancer are more likely to occur in IR/hyperinsulinemic patients, according to reports [3]. Research indicates that there is a strong association between insulin resistance/hyperinsulinemia and sleep disorders [4]. Insulin resistance and metabolic syndrome are complex metabolic features that are important risk factors for developing cardiovascular disease. They are caused by the interplay of environmental and genetic variables, but the full scope of the genetic background of these disorders is unknown [5]; thus, this review will therefore bring to light those aspects which can make a greater contribution to their prevention and control. As a result of the previous reasons, we summarized the symptoms of IR [6] in Fig. 1.

2. THE ASSOCIATION OF INSULIN RESISTANCE WITH OBESITY ACROSS ALL SOCIETY GROUPS

The burden of diabetes has significantly increased due to sedentary lifestyles, urbanization, and socioeconomic advancements. Type 2 diabetes mellitus (T2DM) is characterized by elevated blood sugar levels due to the inability of cells in the body to respond to insulin, a condition known as insulin resistance. Diabetes mellitus (DM) is a leading medical and public health problem around the world. In 2014, an estimated 382 million people around the world were affected. A person with diabetes has a 2 to 3 times greater risk of dying from any cause, making diabetes one of the 10 most important deaths in the world. Saudi Arabia has one of the highest levels of diabetes prevalence in the Gulf and the world, at 23.9% [7]. Recently, the bulk of the 422 million people with diabetes worldwide live in low- and middle-income countries, and diabetes is directly responsible for 1.5 million fatalities annually according to WHO reports presented at the end of 2022 [8]. Adipocytokine and other biologically active chemicals, including adipocytokine, are secreted from the highly active endocrine gland, adipose tissue. The results of the study conducted in the Asir region highlighted the fact that the concentrations of four adipokines—adiponectin, leptin, visfatin, and chemerin—were significantly different in the T2DM patient group compared to the controls, with more marked differences seen in the patients who were obese and highly obese. Therefore, it can be inferred that these four adipokines have an important impact on the development, progression, and related T2DM problems [9].

The effect of this syndrome has exceeded the males and females of adults and has become widespread also among children and adolescents which requires more research into the underlying genetic causes. In a study conducted in Jeddah, the prevalence rate of IR among Saudi female adolescents was 7%. The data results revealed that IR is common among those who are obese and overweight; however, it is also found in those who are not obese or with normal BMI. The two risk variables for the metabolic syndrome that were most frequently found among female adolescents were high glucose levels and large waist circumference. The study also demonstrates that this reference population has lower rates of overweight, obesity, and IR than Makkah and Riyadh [10].

3. THE SIGNIFICANCE OF EXTENSIVE INVESTIGATION OF GENETIC VARIANTS IN INSULIN RESISTANCE INCIDENCE

The genetic factors behind RI are poorly understood and thoroughly investigated. Several

polymorphisms associated with RI, gene, correlated gene-phenotype, and chromosomal location are listed in Table 1 [5].

Explaining how the insulin receptor works will shed light on the role of the genes involved in this syndrome. Pancreatic ß cells release insulin, an important metabolic peptide hormone, in response to high blood sugar. The insulin molecule's binding to its corresponding insulin membrane receptor triggers insulin signaling. The intracellular region juxta-membrane of the receptor undergoes conformational changes following this interaction, which results in the autophosphorylation of some tyrosine residues. Subsequently, an intracellular family of effector proteins known as insulin receptor substrate 1 to 4 (IRS-1 to 4) is phosphorylated and activated by the active receptor [11]. The IRS1 protein appears to play a significant role in the pathway, and research on *IRS1* gene polymorphisms revealed that they were associated with insulin resistance, obesity, and T2DM. These activated proteins then bind with the regulatory subunit (p85) of the enzyme phosphatidylinositol 3-kinase to promote glucose absorption [12-15]. An amino acid substitution occurs at codon 972 due to the single nucleotide polymorphism (SNP) (rs1801278) in the *IRS1* gene, the amino acid Glycine (GGG) is changed to arginine (AGG). By examining its correlation with IR and T2DM, the *IRS1* gene variation candidate has earned the most consideration. Yet, there hasn't been a common understanding of how this polymorphism is related to the occurrence of T2DM [16,17]. In a study conducted on the Saudi population between May and December 2014. A total of 143 subjects from both genders, with an average age of 47.2 years (range 35-73 years), subjects were divided into 74 healthy non-diabetic control groups and 69 subjects with T2DM to assess the relationship between IRS1 polymorphism, Gly972Arg, and G972R and IR in the Eastern Province population of Saudi the findings did not support the association between the IRS1 Gly972Arg polymorphism and T2DM among Saudis from the Eastern Province [18]. In conclusion, our analysis highlights the fact that healthy lifestyle programs that begin in early childhood provide a better preventative strategy to maintain metabolic control and children's health.

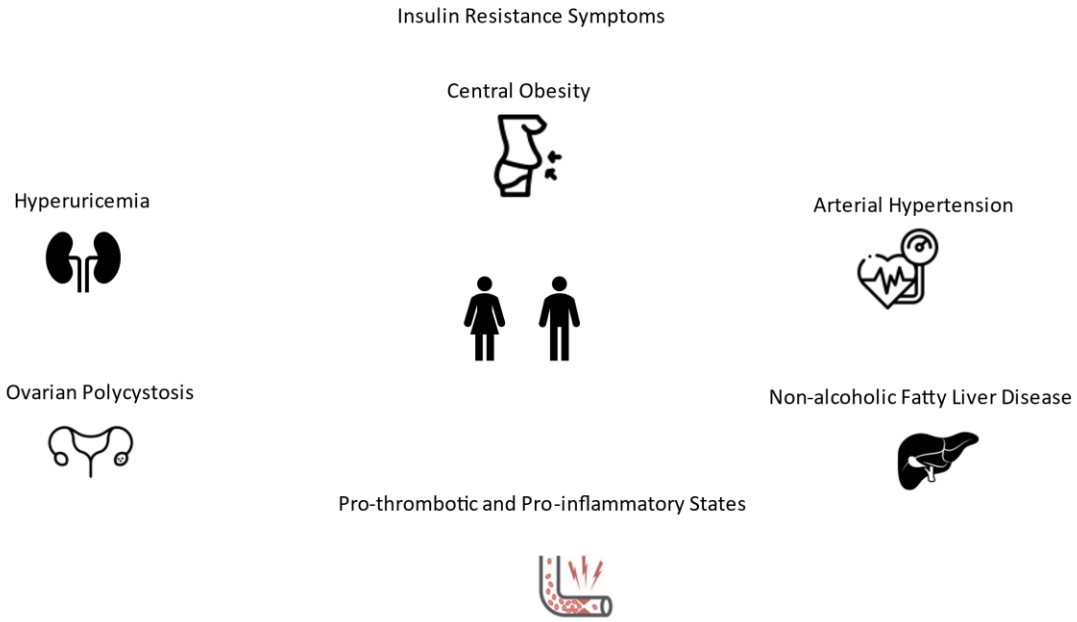

Fig. 1. Symptoms of insulin resistance among males and females. Adapted from Sookoian and Pirola, [6]

Table 1. Variants associated with insulin resistance, gene, the correlated phenotype of the gene, and chromosome locations

N	SNP	Gene	The correlated phenotype of gene	Chromosome
1	rs2943641	*IRS1*	CORONARY ARTERY DISEASE	2
2	rs780094	*GCKR*	[Fasting plasma glucose level	2
3	rs1260326	*GCKR*	QTL 5]	2
4	rs6723108	*TMEM163*	Leukodystrophy,	2
5	rs998451	*TMEM163*	hypomyelination, 25	2
6	rs579060	*ABCB11*	-Cholestasis, benign recurrent intrahepatic, 2 -Cholestasis, progressive familial intrahepatic 2	2
7	rs13081389	*PPARG*	-Carotid intimal medial thickness 1 -Insulin resistance, severe, digenic -Lipodystrophy, familial partial, type 3 -Obesity, severe -[Obesity, resistance to] -{Diabetes, type 2}	3
8	rs146816516	*MBNL1*	Myotonic dystrophy	3
9	rs17046216	*SC4MOL*	Microcephaly, congenital cataract, and psoriasiform dermatitis	4
10	rs972283	*KLF14*	Metabolic phenotypes	7
11	rs1208	*NAT2*	[Acetylation, slow]	8
12	rs76822696	*RALYL*	Highest expression in brain	8
13	rs16912410	*RALYL*		8
14	rs62526240	*RALYL*		8
15	rs55752635	*RALYL*		8
16	rs301	*LPL*	-Combined hyperlipidemia,	8
17	rs295	*LPL*	familial -Lipoprotein lipase deficiency -[High density lipoprotein cholesterol level QTL 11]	8
18	rs77244975	*CTNNA3*	Arrhythmogenic right ventricular dysplasia, familial, 13	10
19	rs7903146	*TCF7L2*	{Diabetes mellitus, type 2, susceptibility to}	10
20	rs964184	*APOA1/C3/A4/A5*	-Hyperchylomicronemia, late-	11
21	rs2266788	*APOA5*	onset -{Hypertriglyceridemia, susceptibility to}	11
22	rs2075290	*ZNF259*	Growth restriction, hypoplastic kidneys, alopecia, and distinctive facies	11
23	rs35767	*IGF1*	Growth retardation with deafness and mental retardation due to IGF1 deficiency	12
24	rs11065987	*BRAP*	Carcinogenesis	12
25	rs7979473	*HNF1A*	-Diabetes mellitus, insulin-dependent, 20	12

N	SNP	Gene	The correlated phenotype of gene	Chromosome
			- Hepatic adenoma, somatic - MODY, type III - Renal cell carcinoma - {Diabetes mellitus, insulin-dependent} - {Diabetes mellitus, noninsulin-dependent, 2}	
26	rs7964157	*KSR2*	MEK's phosphorylation	12
27	rs8050136	*FTO*	- Growth retardation,	16
28	rs9923233	*FTO*	developmental delay, facial dysmorphism - {Obesity, susceptibility to, BMIQ14}	16
29	rs173539	*CETP*	-Hyperalphalipoproteinemia - [High-density lipoprotein cholesterol level QTL 10]	16
30	rs73989312	*CA10*	Catalyze the reversible hydration	17
31	rs73989319	*CA10*	of carbon dioxide	17
32	rs12970134	*MC4R*	- Obesity (BMIQ20) - {Obesity, resistance to (BMIQ20)}	18
33	rs4420638	*APOC1*	Pseudogene	19
34	rs12721054	*APOC1*		19
35	rs10401969	*SUGP1*	The highest expression was detected in the testis	19
36	rs753381	*PLCG1*	Activation of phosphatidylinositol-specific phospholipase C (PLC) enzymes	20

4. THE ROLE OF EPIGENETICS MARKS IN THE INTERACTION OF SOCIOECONOMIC LIFESTYLE WITH GENETICS IN INSULIN RESISTANCE

Studies on the molecular level found that epigenetic modifications may explain the interaction between genetics and environmental factors, especially in complicated disorders such as IR, firstly, the somatic cells usually have the same nucleotides sequence while the pattern of different cell types may have various expressions which influence the gene activity according to the effect of epigenetic mechanisms. Epigenetics reorganize chromatin into regions like euchromatin, heterochromatin, and nuclear compartmentalization resulting from changes in regulatory proteins and the presence of non-coding RNAs, DNA methylation, and histone post-translational changes by specific enzymes which are reflected as IR and other disorders. However, some epigenetic alterations may be reversible [19]. Identical twins' studies found that there is an environmental exposure implicated in epigenetics aspects, especially in hepatic epigenome either this exposure is long-term like in utero, or short-term like the lifestyle [20]. Previous studies found that insulin sensitivity and blood glucose are affected by the circadian rhythm along with an epigenetic gene regulation which is seen as altering in DNA methylation in night shift workers [21]. However, experiments conducted on humans found that the DNA methylation level tuned to benefit the body in a crucial way in specific loci in the case of exercise, weight loss by diet, or bariatric surgery [22].

5. IS MITOCHONDRIAL DNA AFFECTED BY INSULIN RESISTANCE?

Mitochondria are considered a very important organelle and primary metabolic platform of the human cell since it participates in genetics and epigenetics regulation[23] The result of previous studies conducted on IR patients showed that there are dysregulation and an increase of Mitochondrial DNA (mDNA), especially in a promotor region of mitochondrial COX7A1 and NDUFB6 [24,25] Another epigenetic investigation of the mitochondrial genome's D-loop region, which regulates mDNA replication

and transcription as well as nucleoid organization, found a substantial increase in DNA methylation in insulin-resistant people [26].

6. THE INTERFERENCES OF INSULIN RESISTANCE PATIENTS' IMMUNE IN THE SUSCEPTIBILITY TO INFECTIOUS DISEASES

It is common for diabetic patients to experience changes in healing latency resulting from modifications in the amounts of collagenase and growth factor secretion and increased susceptibility to newly emerging contracting [27]. In addition, infectious diseases, including those caused by viruses like the coronavirus 2 (CoV2), the influenza A virus, the hepatitis B virus, and bacteria like *Chlamydophila pneumoniae, Haemophilus influenzae, and Streptococcus pneumonia* [28] Herein, we illustrate this susceptibility by linking the alternation in the immune system and the hyperglycemia in IR patients which associated with declines in humoral immunity, decreased neutrophil and T cell activity, decreased inflammatory cytokine release [29]. In IR status the human body creates stress (catecholamines via β-adrenoceptors) leading to increasing of pro-inflammatory response (cytokines including tumor necrosis alpha-factor, IL1, IL6) which in turn leads to a repetitive cycle entering a patient in a hypercaloric fatty diet hence, the body will elevate blood glucose, fatty acids, glycerol, and other local vascular effects by increasing the metabolism of glycogen and triglycerides. Eventually led to immunosuppression [30,31]

7. WHAT TRIGGERS FIRST COVID-19 OR INSULIN RESISTANCE?

The answer to this question is to assess the comorbidity of insulin resistance concomitant with COVID-19 because COVID-19 patients have a high risk of death, but this does not contradict the other part of the question whereas the patient with COVID-19 was susceptible to developing an IR [32] Patients with a history of IR exhibit a decline in immunological function, which has a knock-on effect on endothelial function and ventilation [33] To understand the relationship between those two diseases we summarized the paces of this development in Fig. 2 which eventually showed that COVID-19-causing of IR. Along with this, IR patients have more susceptibility to being affected by COVID-19- [32,34].

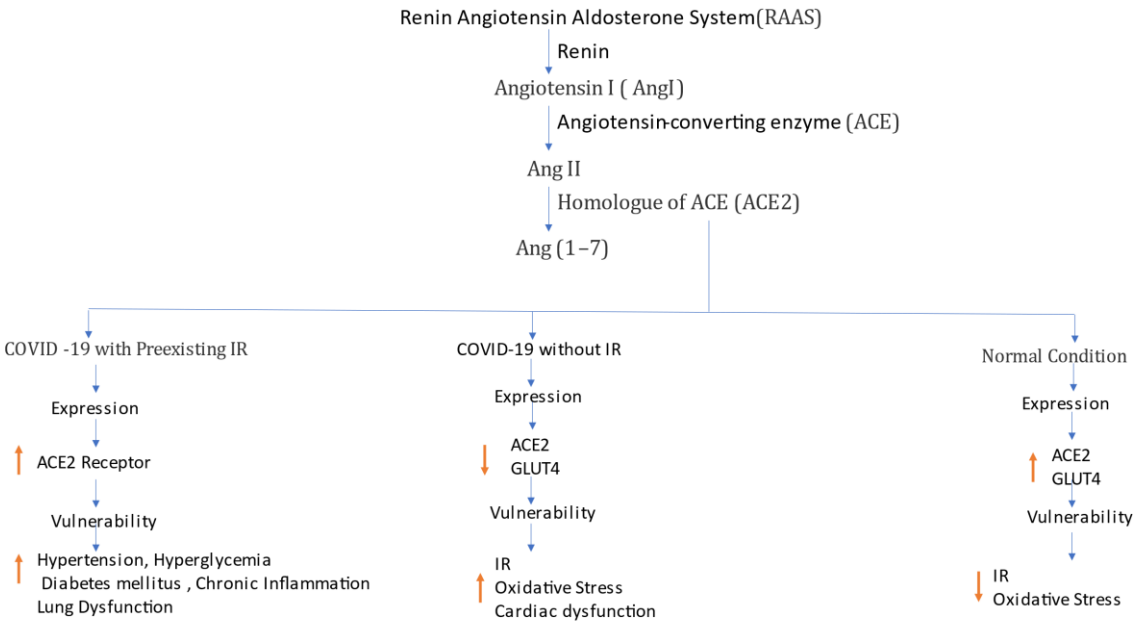

Fig. 2. The pathway of Renin Angiotensin Aldosterone System and the relationship between COVID-19 and IR. This scheme is adapted from Govender *et al.*, [32]

8. ARE THE TREATMENTS AVAILABLE IN THE MARKETPLACE EFFECTIVE IN OVERCOMING INSULIN RESISTANCE?

The fundamental reason behind the emergence of insulin resistance is the failure of the receptors, which in turn affects cell signaling and thus causes a disturbance of the entire metabolic process. Therapeutic methods depended on several approaches that would stimulate cells to return to insulin sensitivity throughout the activation of the intracellular B subunit of the insulin receptor. In addition to improving the action of insulin by phosphatase and serine kinase inhibitors which normally prevent the cessation of signaling tyrosine kinase. It also included a means to improve the activity of phosphatidylinositol 3-kinase and other elements involved in insulin signaling processes, considering the elimination of the negative effects of cytokines. Further additions of cofactors, coenzymes, and hormones were also observed to help cells regain their semi-normal state in terms of insulin response [35] Harnessing the solutions resulting from the development of knowledge offers the possibility of a simultaneous therapeutic attack on multiple fronts.

9. CONCLUSION

Through this review, we found that the causes of IR, whether acquired or genetic, affect all spectrums of society, also the solutions proposed to overcome this disorder contribute to reducing IR. However, Future research may establish additional novel mechanisms of action and provide recommendations for lifestyle interventions like increasing physical activity and insulin sensitivity.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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