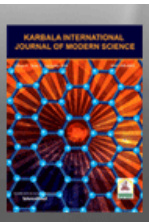

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A Systematic Mapping Study on the Risk Factors Leading to Type II Diabetes Mellitus

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A Systematic Mapping Study on the Risk Factors Leading to Type II Diabetes Mellitus

Abstract

Diabetes is one of the most common diseases that has had devastating effects on the general population. It is also among the most popular research trends in modern medicine. Thus, due to the complexity and desirability of this particular affliction, there is a lot of demand towards understanding this disease better, so that it can pave the way towards better solutions in combating diabetes. The aim of this review is to provide a categorization of the risk factors leading to Type II Diabetes. In order to provide a justification for the type of diabetes, an explanation is provided which covers the other types of diabetes and their relative infliction rate. Once the basics understanding of diabetes established, the various aspects that increase the risk of Type II Diabetes (T2D) can be classified. Several different facets are studied in order to come up with a novel classification of the disease. The classification divides the risk factors into sociodemographic and pathophysiological attributes. The major affecting attribute is identified to be genetics, as it is intertwined with other attributes. With the use of bioinformatics, advanced gene sequencing techniques can be applied that would enable the identification of patterns more closely affecting Type II Diabetes. These patterns can be cross-analyzed with pre-existing conditions in order to identify similarities and possible risk factors from other diseases. Ultimately, this classification provides a deeper understanding of the factors affecting Type II Diabetes.

Keywords

Diabetes, Type II Diabetes Mellitus, Classification, Systematic Mapping, Diabetes Risk Factors

Cover Page Footnote

- This research are by coopertion between UTM University Biomedical engineering and Health science school and Babylon University faculty of medicine.

1. Introduction

Diabetes mellitus is a disease comprised of a group of symptoms, which have been observed and identified since the early days of medicine [1]. The first reported observation of these symptoms was over 3000 years ago in Egypt [2]. Over the last few millennia the disease has been studied more intensely, and its definition and related sub-categories have since expanded. The main breakthrough was during the 18th century when chemistry was used as a diagnostics tool [3]. New discoveries were made in every century that allowed for a better understanding of the disease. However, each time there were new identifiers or causes that were contributing to its risk factor. Even though the disease has been studied for nearly four millennia, there is no documented evidence report the cure discovered types of diabetes. Better diagnostic tools have allowed us to discover the widespread affliction of this disease. Based on the renal data reported from US, there is an indication that the disease is only growing and becoming more widespread [4,5]. Other countries have also reported to having a similar rate of increase in diabetic cases [6].

Although there are several types of diabetes, Type II Diabetes is considered to be the most prevalent. Thus, identifying its contributing factors becomes an essential step towards finding preventative measures and treatments for hindering the growth of the disease [7].

There are several existing reviews that aim to identify risk factors based on a specific criterion [8−10]. However, there is a lack of studies that collects information from different aspects of the disease, which would ultimately provide a better overview of the interlaying factors and their relationships with one another. Thus, the aim of this study is to perform a systematic study that collects most of the relevant material addressing the issue of Type II diabetes. This systematic categorization is set apart by the fact that it collects data on both physiological and sociological factors that are reported to affect the disease. These studies are then each analyzed and then synthesized into a collective categorization which aids in understanding the disease better.

This paper is structured by first focusing on the main classifications of diabetes, and understanding the prevalence of each type. The section that follows would then focus on proposing a classification for Type II Diabetes, which is considered to be the most prevalent type of the disease. Once all the factors are laid out, a discussion takes place on understanding and connecting the various factors identified and collected. Finally, a conclusion is made based on the analyzed information.

2. Diabetes classification

Diabetes refers to a group of metabolic disorders characterized by high blood glucose levels resulting from defects in insulin secretion, insulin action, or both [11]. In 1936, Himsworth conducted research that ultimately led to the separation of debates types [12]. Diabetes mellitus has become one of the most researched diseases in medical history, due to its prevalence and lack of a concrete cure [5].

Traditionally, diabetes is divided into two types (Type 1 and Type 2) [13]. However, the disease is far more complex than that, and it can manifest differently, based on a different set of contributing factors. Thus, the separation and distinction are important in order to concentrate and focus the efforts regarding its identification and subsequent treatment [14]. However, some of these have overlapping symptoms or conditions. For the sake of simplicity, we categorize diabetes into five categories. The main two categories are Type 1 and Type 2 Diabetes (T1D and T2D) [15]. Genetic based diabetes such as Maturity onset diabetes of the young (MODY) and others such as Latent Autoimmune Diabetes of Adulthood (LADA) are among the other sub categories of diabetes [16,17]. There are also other lesser-known categories such as Type 3 Diabetes that is unique to women during their pregnancy [18]. These categories are depicted and classified in Fig. 1.

Fig. 2 illustrates the percentage of each of these types and a broad view of how prevalent they are relative to one another. Based on the observed percentages, T2D is the most prevailing form of diabetes, which encompasses almost 80% of the reported cases. This form of diabetes one of the most public long-term endocrine disease is Type 2 Diabetes Mellitus (T2DM), which characterized by hyperglycemia resulting from reduced insulin emission and/or insulin resistance [19]. There are observations that related T2D towards the increase of obesity around the world. The rate of obesity (defined as an individual with a BMI higher than 25), has increased by 60% in the last 30 years in the UK among males older than 15 years of age [20]. The increase in obesity has environmental and social

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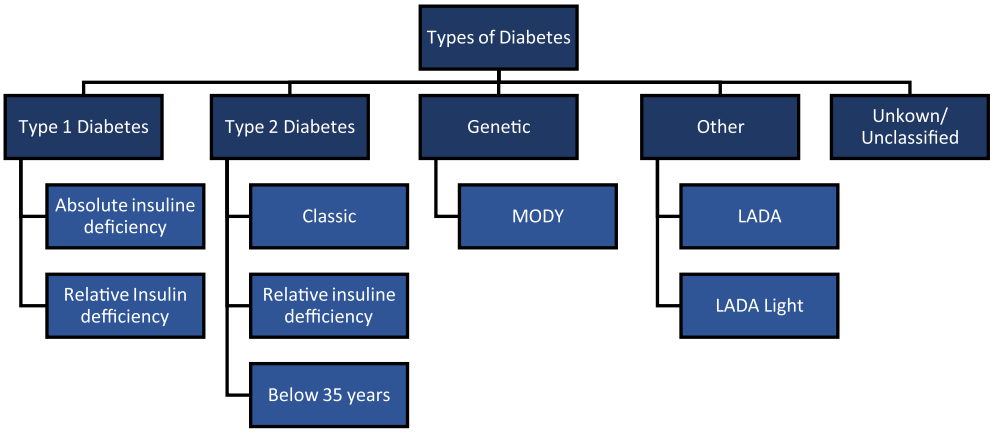

Fig. 1. A Types of diabetes and classification.

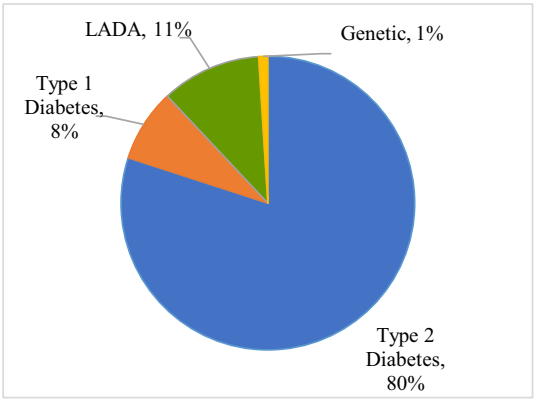

Fig. 2. A pie chart depicting the prevalence ratio of the main types of diabetes.

impacts, as lives have become more sedentary, but at the same time, people consume high energy foods filled with simple carbohydrates that ultimately lead to high-calorie deficit [21–23].

3. T2D contributing factors

There are several aspects of T2D that are required to be studied in order to fully understand the contributing factors [24,25]. Some of these aspects relate to the demography of those afflicted, and others relate to the physiological aspects of the disease. To gain a better understanding of the disease on how it operates its effect on age and race need to be further researched and observed.

A small controlled sample is observed in Fig. 3, which illustrates the prevalence of T2D among the ages of 10–100 in New York City. These observations were reported by New York State Department of Health Statewide Planning and Research Cooperative System and they were primarily measured by counting the number of diagnosed patients that had visited any type of emergency department between the years 2011 and 2015 [26–28]. These results indicate that there an underlying factor that relates to the prevalence of diabetes.

3.1. Classification of T2D risk factors

In order to adequately classify the risk factors related to Type 2 Diabetes, there needs to be an understanding of its two main related facets. These facets are rarely addressed or studied together and are often mentioned or viewed in different instances of research [29–33]. Thus, the proposed classification divides the factors into two main groups of sociodemographic attributes and pathophysiological attributes. This classification is illustrated in Fig. 4.

One of the main and biggest factors that are often overlooked is sociodemographic attributes. This classification refers to several sub-factors such as age, gender, race, ethnicity, and overall demographic related attributes. The other facet of this classification is the pathophysiological which is not separate from the sociodemographic, but rather a different perspective and focus. This classification focuses on risk factors such as genetics, thyroid abnormality, and insulin resistance, among others.

3.1.1. Race

There are several studies that indicate race as one of the several sociodemographic factors that have an effect on the susceptibility of T2D [25,34–36]. This is further reinforced in Fig. 3 which encompasses Asians under

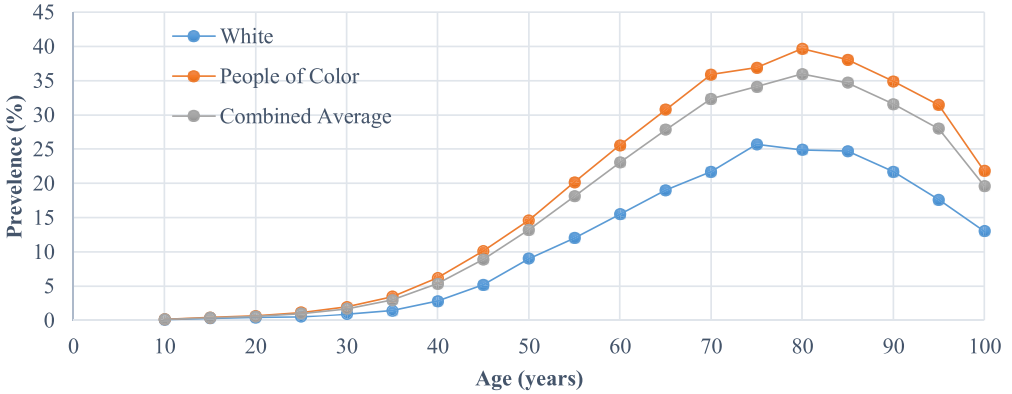

Fig. 3. Estimate prevalence of Type 2 Diabetes between ages 10 to 100 years in New York City from 2011 to 2015.

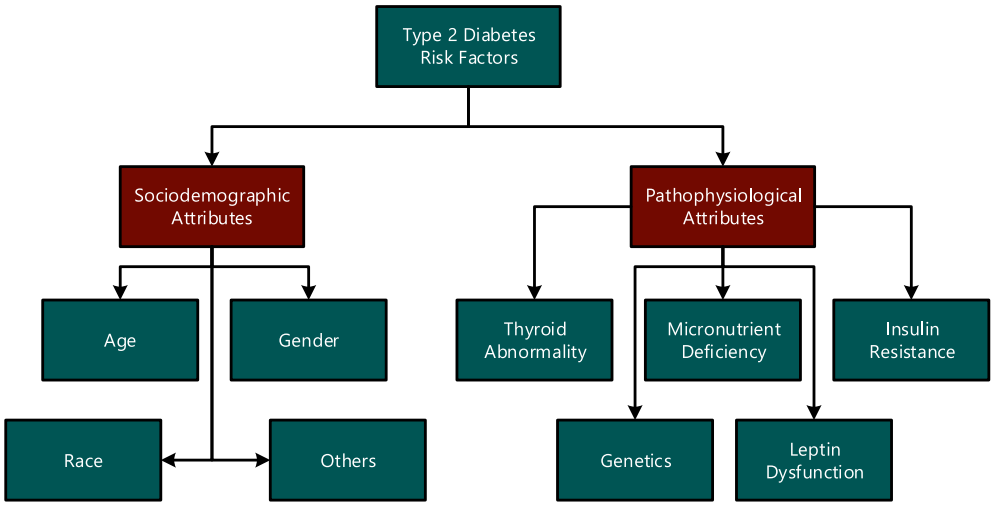

Fig. 4. Type 2 Diabetes Risk Factors.

the people of color average, which indicates to have a higher risk of Type 2 Diabetes than white Americans. This could be attributed to cultural differences between the races, as some consume certain food groups more than the others. There is also the fact that genetics plays a role in the disease, as some races are more susceptible to certain diseases than others [37–40].

3.1.2. Age

Regarding age, there is an indication that as the age rises, the number and percentage of people inflicted with Type 2 Diabetes have also increased [41–43]. However, upon closer inspection, it is clear that at some point there is a fall off. The age that the chart has shown (Fig. 3) to have the highest susceptibility age at 80 years old for people of color, and 75 for people with white skin. After this age, there is a decline in the percentage of people with Type 2 Diabetes. This can be caused by many factors; one such phenomenon is that patients with Type 2 Diabetes usually do not survive longer than 80 years old. However, maintaining a healthy lifestyle makes one less susceptible to the disease, and thus, disproportionately allows for a lower percentage of Type 2 Diabetes [44].

3.1.3. Gender

Regarding gender, research has shown the men are more susceptible to Type 2 Diabetes than women [45]. This has mainly pathophysiological reasons which are further discussed in the related sections. However, to illustrate the difference, Fig. 5 shows the main percentage which is 65% for biological males and 35% for biological females. This means that men are more at risk of Type 2 Diabetes than women [46].

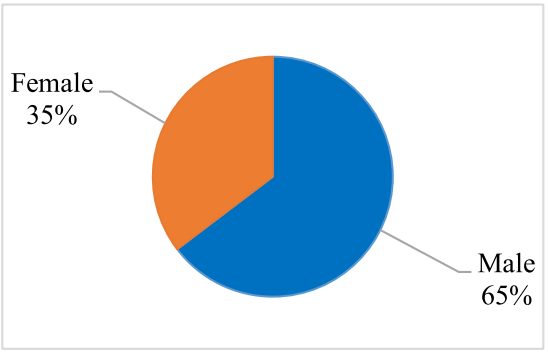

Fig. 5. Gender ratio on Type 2 Diabetes.

3.1.4. Others

There are some other contributing sociodemographic attributes such as occupation, religion, and other lifestyle matters which also heavily impact the risk of Type 2 Diabetes. However, they are not the main focus of this study [47,48].

3.1.5. Genetics

There are several established kinds of research that indicate that genetics has a major role in the development of T2D. However, the degree of its effects is under research, as some have a claim it to have as much as 80% effective when it comes to heritability, while others have concluded that the effects of genetics are as low as 25% [49–51]. However, regardless of this issue, the facts are clear that genes are extremely important when it comes to their effect on T2D.

3.1.6. Thyroid abnormality

The most common endocrine disorders are Dysfunction of the thyroid gland and carbohydrate metabolism such as diabetes mellitus (DM) and prediabetes [52]. The prevalence of thyroid dysfunction in T2D patients was reported to be 12.3% in Greece and 16% in Saudi Arabia [53,54]. The higher the flowing levels of insulin because expanded thyroid multiplication. And the clinical appearances are the bigger thyroid volume and the arrangement of knobs. In this manner, the thyroid organ gives off an impression of being another casualty of the insulin opposition disorder [55–57].

3.1.7. Leptin dysfunction

Another sub-factor is the effect of Leptin. Leptin discovered in 1994 as a regulator of body weight and energy balance that produced mainly in the adipocytes of white adipose tissue [58]**.** There is a suggestion that defects or dysfunction in leptin signaling may contribute to the etiology of diabetes and raise the possibility that either leptin or downstream targets of leptin may have therapeutic potential for the treatment of diabetes [59,60].

3.1.8. Insulin resistance

A variety of clinical disorders are accompanied by increased fasting plasma insulin concentrations Insulin resistance (IR) and impaired insulin secretion is a distinctive characteristic in Type two diabetes mellitus [61]. The presumption was made, based on many studies of Caucasian subjects, that insulin resistance triggers T2D, which is compensated originally by the increased β-cell response, which finally causes T2D due to the collapse of pancreatic β-cells [49,52,62]. Insulin resistance occurs before decreased insulin production and needs to be identified early, by one of the methods to measure insulin resistance [50,51,63,64].

3.1.9. Micronutrient deficiency

The lack of supplements and nutritional elements in the body has been shown to cause complications that can lead to several underlying conditions in the body [65]. For instance, there is an established relationship between vitamin deficiency and obesity, which in turn has a direct impact on diabetes and insulin resistance [66]. Among the current researches published, it has been established that Vitamins A, C, D, and E have the highest impact on diabetes, while minerals such as Zinc, Copper, Selenium also seem to be related to insulin regulation and thus affect diabetes in some shape [67].

The impact of micronutrient deficiency on the body causes effects that inadvertently accelerate diabetes. This is because of the lack of these minerals and micronutrients affects the body functions differently, and causes them to either not function or underperform. This is seen based on the results in Fig. 6, in which the highest affecting vitamin is Vitamin D, followed by Vitamin C [68].

3.2. Genome of the type II diabetes

The expression of the genome, are also affected by The environment thus ultimately the phenotype, via the epigenome, the phenotype is mutated by epigenetic modifications of gene expression by mechanisms along with methylation of DNA, posttranslational modification of histones, or activation of microRNAs, even though the DNA sequence is not changed. These changes to the phenotype can be at the point of the

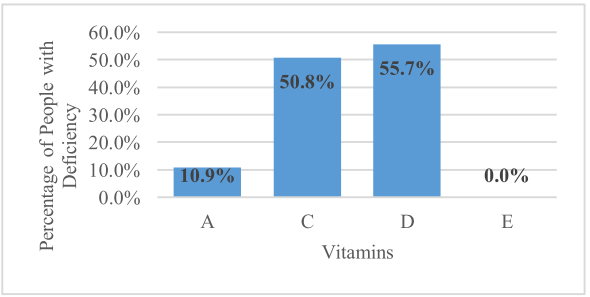

Fig. 6. Percentage of people with vitamin deficiency that suffer from diabetic foot ulcers [68].

entire organism, tissue, or cell. It is tempting to theorize that environmental factors such as diet and exercise can change the level of DNA methylation and thereby cause changes in gene expression until nowadays there is no evidence support that DNA methylation contributes to the increase in T2D.

The risk of SNP is directly relative to the number of exons as the hazards of exposure for mutations is high. The risk of SNP is indirectly relative to the length of the gene since greater length with a higher number of introns poses a lesser risk of mutation in the protein-encoding. Therefore, the risk for the protein encoding genes was derived as a ratio of the number of exons to the length of the gene. insulin hormone which plays a main role in the utilization of glucose by the peripheral tissues thus reducing the blood glucose level, it can be noted that the INS gene has a direct relation to diabetes as the gene encodes the insulin hormone. It was observed that INS gene located on chromosome 11 has greater susceptibility to mutation with the risk ratio value of 0.0020, followed by PAX4 gene located on chromosome 7 with a value of 0.0015 and SUMO4 gene located on chromosome 6 with a value of 0.0014. The relative risk for the rest of the genes was presented in Fig. 7. Thus mutation in INS gene may lead to elevated blood glucose levels [65–68].

4. Discussion and analysis

The aforementioned studies confirm the effect of IR which may lead to DM but still research needed to detect the parameters which may affect the IR and find out more about the relationship between these two disorders which effect on whole metabolic Pathway.

Hyperglycemia, insulin deficiency, and development of complications can be considered extremes of the diabetes spectrum which is similar to T1D, and T2D share a few manifestations in underlying physiology. However, the genetic degeneration of T1D and T2D widely differ, with very few T2D susceptibility loci showing an association with T1D. Notable exceptions include the Peroxisome proliferator-activated receptor gamma (PPARG) Pro12Ala variant, Melatonin receptor 1B (MTNR1B), Hepatic Nuclear Factor 1 Alpha (HNF1A), Family Zinc Finger 3 (GLIS3), 6q22.32 and

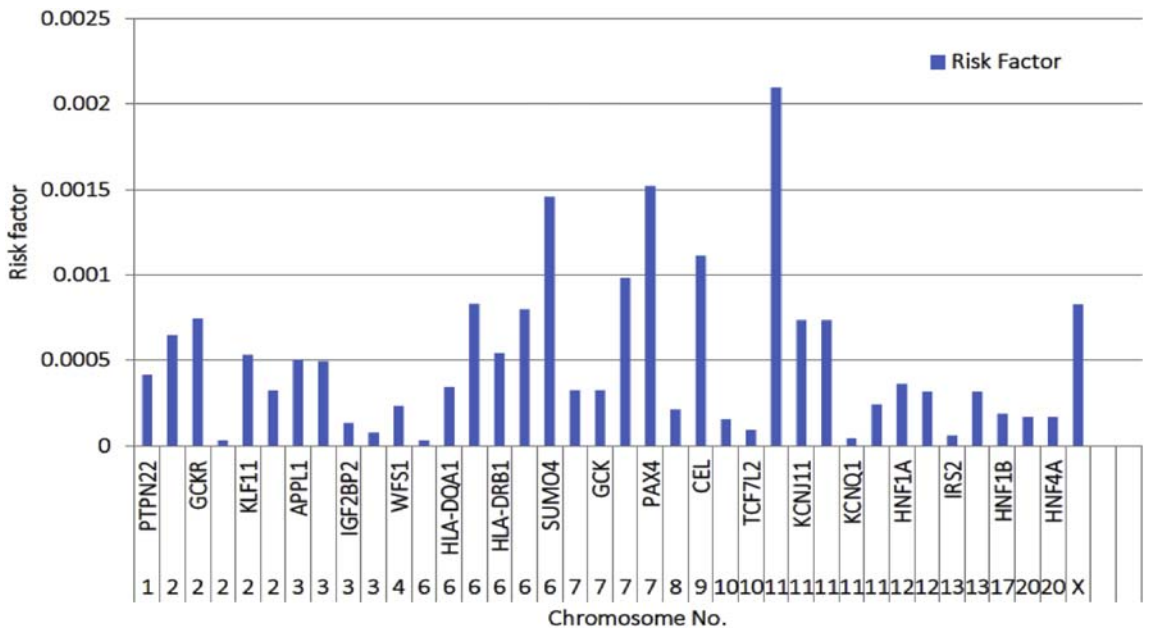

Fig. 7. Relative risk factor for the protein encoding genes. Risk factors were calculated as ratio of number of exons to gene length.

novel loci near the (major histocompatibility complex) MHC, which harbor the (human leukocyte antigen) HLA class II genes associated with about half the T1D risk [65–67,69]. Based on these studies, the mechanisms underlying T1D and T2D appear to be alone distinct. The distribution of T2D risk SNPs should be more random in a T1D patient; however, this does not seem to be the case. The protection from T1DM by strongest T2D-SNP in the TCF7L2 gene. T1D risk variants for BCAR1, GLIS3, and RAD51L1 were protective for T2D whereas, for those in C6orf173, COBL, and C10 or f59, the effects were coincident [70]. Also, it has been reported that APOC3 haplotypes increase the risk of T1D; however, the same variants increase the risk of T2D in lean carriers while having a protective effect in overweight carriers [71]. Common variants in SLC30A8 are associated with an increased risk of TYPE 2 DIABETES, and rare variants with a protective effect [72,73]. In new-onset T1D patients, a mystery was also found, SLC30A8 be a major autoantigen trigger 60%–80% autoantibodies [74].

As for micronutrient deficiency, there is a major indication that both the lack of certain vitamins and minerals can increase the risk of getting diabetes [75]. Both due to the direct and indirect effect of these elements.

Vitamin D deficiency was the most common deficiency observed, and based on the results of previous studies it seems to be a major factor [76]. However, there are several possibilities that would explain this phenomenon. Most of the studies that measured Vitamin D deficiency were performed on diabetic patients. In a study conducted among 912 subjects (429 T2D cases and 483 non-diabetic control), it was found that Vitamin D deficiency was reported in T2D (91.4%) and nondiabetic subjects (93.0%), its role in hemoglobin glycation and IR could not be established [77]. It is worthy of note that depletion in Vitamin D status might not only be an indicator of ill health but could also be an indicator of the individual lifestyle pattern ranging from indoor working with restriction to sunlight exposure, low visibility, and poor dietary habits. In addition, Vitamin D deficiency was found to affect insulin synthesis and secretion in human/animal models of DM, suggesting its role in the etiology and pathogenesis of both types of DM [78].

Typically, in people with obesity, there is a tendency of less physical exercise and thus, there are reported to get a lesser value of Vitamin D from the Sun. This ultimately affects the system negatively, as the lack of mobility ultimately leads to further complications and issues. The importance of Vitamin D remains of undisputed importance for Diabetes. Thus, the deficiency is considered to be one of the more critical risk factors.

Zinc, Selenium, and Iron have also had several studies conducted on them, which ultimately concluded that both Zinc and Selenium have the highest effect on diabetes, as these minerals are used for the synthesis of certain proteins in the body that ultimately regulates insulin [79]. Thus, their existence is necessary, and therefore, the lack of them can increase the risk of diabetes. Most interestingly studies indicate that supranutritional Selenium intake and high plasma Se levels are possible risk factors for the development of T2D, pointing to adverse effects of Se on carbohydrate metabolism in humans. Also, an increase in plasma Se levels might be a consequence and cause of diabetes. Besides Selenium, a number of metal ions (vanadium, copper, zinc, and cadmium) are known to trigger insulin-mimetic effects by activating AKt and other kinases of the insulin signaling cascade such p70S6. It is postulated that PGC-1α serves as its molecular switch linking Se and carbohydrate metabolism [80].

5. Conclusion

In conclusion, a systematic study was conducted on the risk factors (also known as contributing factors) behind Type 2 Diabetes. This answered two main questions. First, to categorize the different types of diabetes. This was done by performing and in-depth study on the various aspects of diabetes, and it was concluded that there are generally two main categories and several other smaller categories. Type 2 Diabetes was the most inflicted among all. Hence, the focus is shifted towards this type of diabetes. The second research question focused on categorizing the main risk factors behind Type 2 Diabetes. Through extensive research and review, two categories were proposed. Sociodemographic, and pathophysiological attributes. Sociodemographic attributes focused on collective issues such as age, gender, race, and others which heavily influenced the prevalence of having Type 2 Diabetes. Men for instance were more prevalent than women, which were disproportionately affected by the disease. The race also played a main role, however, this could have cultural and lifestyle implications, rather than racial genetics. The next category of pathophysiological attributes focused on internal issues, such as hereditary factors (genetics), insulin resistance, thyroid abnormality, and leptin dysfunction. These were each study and presented with related papers and references.

The two most important attributes that increase the risk factor of Type 2 Diabetes were Genetics and Micronutrient Deficiency. Genetics enables pre-existing conditions that were observed in race, gender, and environment to have effects on human physiology, which ultimately would make certain bodies more susceptible to Diabetes. Micronutrient deficiency also indicated that the lack of certain vitamins, such as Vitamin D, could have a huge effect on the occurrence of Diabetes, as this vitamin is responsible for the synthesis of certain proteins inside the body that can lead to obesity and diabetes if not balanced and addressed. Same with certain minerals such as selenium and zinc, which are required for your body to synthesize insulin, and a deficiency in them can cause a chain reaction, which ultimately leads to Type 2 Diabetes, as well as some other complications.

These were ultimately the main findings of this systemic review and categorization. This form of categorization and classification would allow future researchers to focus their efforts on certain aspects of the risk factors and identify all related issues that stem from their existence. Using bioinformatics and, advanced gene sequencing techniques can be applied that would enable the identification of patterns more closely affecting T2D. These patterns can be cross analyzed with pre-existing conditions in order to identify similarities and possible risk factors from other diseases.

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