



Current Trend of Nutrigenomics of Geriatric Type 2 Diabetes

**Viola A. Nwachukwu Nicholas-Okpara¹, Ifesinachi Anastacia Utazi^{2*},
Chika Scholastica Ezeanyanaso³, Blossom Ita⁴, Adaeze Joy Ukaba⁵
and Maryam Olanshile Adegboyega^{1,6}**

¹Nutritional and Toxicology Division, Food Technology Department, Federal Institute of Industrial Research, Oshodi, Nigeria.

²Food Science and Technology Department, Abia State University, Abia State, Nigeria.

³Chemical, Fibre and Environmental Technology Department, Federal Institute of Industrial Research Oshodi, Nigeria.

⁴Biotechnology Department, Federal Institute of Industrial Research Oshodi, Nigeria.

⁵Food Science and Technology Department, Federal University of Technology Owerri, Imo State, Nigeria.

⁶Animal and Environmental Biology Department, University of Benin, Edo State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus type 2 (T2DM) is a growing burden in the global public health and economic systems. Older adults are more than two times predisposed to T2DM and they are more likely to develop T2DM-related complications. A complex interaction of genes, diet and environment is a key factor in the development of this chronic metabolic disorder. With nutrigenomics, researchers are beginning to understand this interaction. This review aims at examining gene-diet relationships concerning T2DM as well as the applications and potential of nutrigenomics in managing geriatric type 2 diabetes. Several genome-wide association studies have documented susceptibility genes for T2DM. Among these genes are TCFL2, PPARGy, CAP 10, ADBR3, DPARGCIA, and ENPP genes. Several bioactive compounds in foods have also been shown to act as switches on T2DM

susceptibility genes, aiding in the progression or inhibition of the disease. These findings have helped in developing nutritional recommendations that are relevant to the management of T2DM particularly in carriers of these susceptibility genes. In this comprehensive review, the current trends, and prospects of nutrigenomics as an intervention for geriatric diabetes is explained.

Keywords: Nutrigenomics, bioactive compounds; type 2 diabetes; older adults; susceptibility genes; and genes diet interaction.

1. INTRODUCTION

Diabetes mellitus type 2 (T2DM) continues to be a heavy burden in the public health system. Diet, age, and genetics have been reported in several studies to be associated with the progression of this disease and development of comorbidities.

Nutrigenomics is the branch of science that studies the influence of food on gene expression. In the past years, research has confirmed that the human genome is greatly similar between individuals and some genetic entities known as Single nucleotide polymorphisms (SNPs) are responsible for the variation in behaviour and genetic responses to the environment (nutrition inclusive). This explains the higher susceptibility of individuals to certain diseases.

In recent years, several studies are aiming to discover and understand the gene-nutrient interaction and its effects on the development or mitigation of diseases on a molecular level. This is leading researchers to understand the mechanisms of various diseases pathogenesis and the development of potential interventions to manage diseases.

In this intensive review, we examined the current trends and the prospects of nutrigenomics in managing the incidence of diabetes in older adults Fig. 1.

1.1 Overview of Geriatric Diabetes

Diabetes is a world leading cause of retinopathy, cardiovascular diseases, kidney dysfunction and lower limb amputation [2]. Aging is a predominant factor of developing T2DM and its complications. Among adults aged ≥ 65 years, as high as 1 in 3 persons have diabetes and 3 in 4 persons have prediabetes; with an even larger proportion of this population undiagnosed [3]. Older adults are over two times predisposed to T2DM and its macrovascular and microvascular complications such as retinopathy, kidney failure, stroke, neuropathy, peripheral vascular disease, and autonomic dysfunction [4]. Besides being a heavy burden on individuals, families and the

health system, diabetes is equally an economic burden. As of 2019, diabetes in seniors aged 60-79 years alone takes up 46% of the world's total expenditure on diabetes, summing up to USD 350.7 billion [5].

There is a high prevalence of sedentary lifestyle and reduced physical activity as aging sets in which leads to loss of lean muscle mass, reduced physical strength, and obesity. A strong link has been established between obesity and the incidence of diabetes. Obesity is characterized by increased deposition of fatty acids on the liver, heart, pancreas and muscle and it is generally observed with increasing waist circumference. The deposited fatty acids produce proinflammatory adipokines that mediate peripheral insulin resistance which is characterized in T2DM [6]. There is also a notable decrease in insulin secretion in older adults. Halim and Halim [7] reported that insulin secretion tends to reduce by 0.7% every passing year and this is due to the increased apoptosis and reduced ability to replace beta pancreatic cells.

Effective treatment of T2DM in this age group has been quite difficult. Older adults are usually poorly represented in intervention studies [8]. Also, older adults struggle with other age-related comorbidities and this may pose an adverse effect due to drug-drug interaction [9]. While struggling to keep blood glucose in control, older adults are also prone to hypoglycemia which results in the higher risk of fall, neurodegenerative diseases such as dementia, neuropathy, stroke, cardiovascular disorder, and death [10]. Many studies have suggested personalized recommendation based on several factors like the presence of other diseases and lifestyle of the individual. Several interventions such as setting glycemic targets, lifestyle modifications, nutrition-based treatments and drug therapy have been used to treat and manage T2DM in older adults [11]. Weight management and regular screening for complications such as retinopathy and kidney diseases were also recommended by WHO [2].

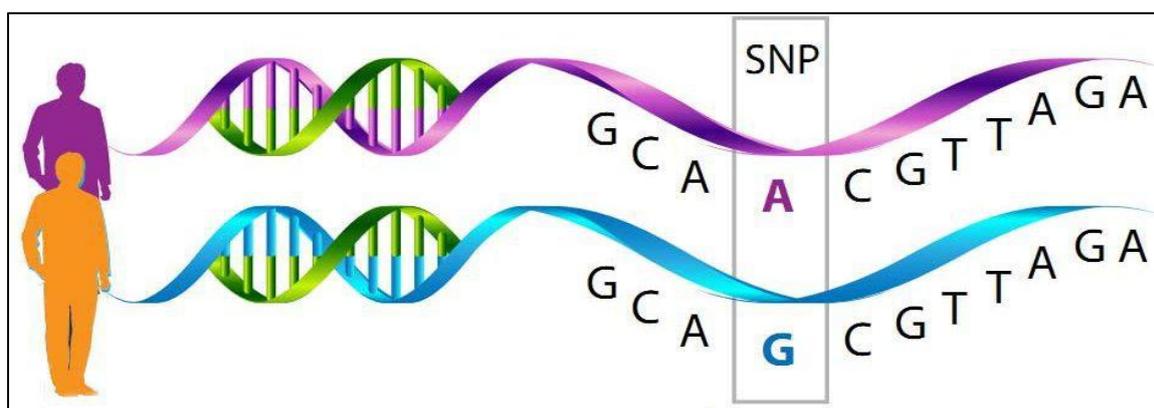


Fig. 1. Simple illustration of human genetic similarities and SNP variation [1]

1.2 Nutrigenomics and Gene Expression

For many years, the roles of genes as risk factors of diseases have been studied. For example, the long non-coding RNA (lncRNA) have been found to regulate many cancer-related indicators such as inducing angiogenesis of tumors, evading tumor growth suppressors and resistance to cell apoptosis [12]. The discovery of genes to be an important factor to disease generation has unlocked a better understanding of some diseases. Various studies in the past years that observed family history of study subjects have confirmed that some individuals are genetically susceptible to certain diseases [13]. These genes are regarded as 'susceptibility genes'. In the study of obesity pathogenesis, 25 susceptibility genes were identified in the 7q36.3 and 8q21.13 regions of the chromosome using a targeted resequencing technology in a case control investigation by Wu et al. [14].

However, several studies have also shown that the expression of a trait is beyond genes alone. Blazer and Hernandez [13] explained that variation in genes may be because of its interaction with other genes or with the environment and evidence of familial aggregation may also represent the exposure to a common environment. An earlier study by Liu et al. [15] proves this theory correct. The study found that obesity results from a complex interaction with the susceptibility genes rather than a single gene. This finding illuminates the fact that other factors such as diet and physical environment play an important role in the phenotypic expression of a gene.

The branch of science that investigates the effect of nutrition on genes on the molecular level is termed nutrigenomics. Since the completion of

the Human Genome project in 2003, several studies have been carried out to investigate the nutrient-gene interaction. Nutrigenomics aims to understand the influence of diet on the genome, the RNA, cellular protein patterns and metabolite profiles and their overall effects. In public health, studying gene-nutrient interaction has particularly helped in identifying the root cause and mechanisms of many diseases. Gene-nutrient interactions have been shown to play a key role in the development or inhibition of several diseases such as food allergy, diabetes, periodontal disorders, cancers, obesity, hypertension, and kidney diseases. For instance, a clinical study observed a significantly increased expression of *FGFR2*, a cancer susceptibility gene, after supplementing the diets of breast cancer patients with soy [16]. Epigallocatechin gallate (EGCG), a polyphenol found in green tea has been reported to reduce the incidence of many cancers through the demethylation of tumor suppressor gene promoters [17]. For celiac disease, gluten peptides contained in wheat stimulate the HLA-DQ2 gene resulting in a chain of reactions that triggers a negative immune response in genetically susceptible individuals [12]. A descriptive, cross-sectional study conducted by Zaki et al. [18] deduced that homozygous carriers of the *APOA2* CC alleles were at higher risk of obesity. The study reported that the CC allele was more common in obese test subjects who had higher BMI, WC, WHR, body fat % and visceral fat. In agreement to this study, an epigenome-wide association study by Lai et al. [19] also confirmed that *APOA2* CC genotype carriers had higher BMI only when they consumed high saturated fatty acid linking the heavy consumption of the unhealthy western diet to metabolic diseases. Koochakpoor et al. [20] suggests that the components of western diets such as soft drinks, high fat dairy food, and

refined carbohydrate may modulate the MC4R gene polymorphism, putting carriers at high risk of metabolic disorders.

This new knowledge has also led to the development of potential therapeutic nutritional interventions such as precision nutrition. Precision nutrition involves the recommendation of unique nutrition for an individual based on the genetic, environmental and lifestyle factors with the aim of achieving optimal health and overall wellbeing [21]. Many studies that have investigated the gene-diet interaction have shown evidence of reduced risk with the avoidance of certain foods. Among such are gluten-free diets recommended for the individuals with celiac disease and Mediterranean diets in place of western diets. The study of gene-diet interaction will help to identify key molecules to help mitigate or reduce the risk of diseases [22].

1.3 Genomics and T2 Diabetes

Type 2 diabetes (T2D) is a metabolic disorder pre-dominant in adults that causes increase of blood sugar in the body which the body cannot absorb usually referred to as insulin resistance. T2D is as a result of interaction between environmental factors such as lifestyle, obesity and a strong hereditary component (genetics). Heredity has long been mentioned to play an important role in the development of T2D. In recent times, advancement in human genetics studies and modern genetics technology has further established the place of heredity in the development of T2D. In recent years, candidate gene studies were the used in identifying genes that are associated with T2D before the introduction of genome wide linkage and association studies [23].

1.3.1 Most relevant T2D susceptibility genes

According to Barroso et al., [24], identification of candidate genes was one of the approach used to identify T2DM susceptibility genes. Recently, novel T2D susceptibility loci were identified through genome wide association in European population. Among the numerous genes associated with T2DM, TCF7L2 emerges as the most relevant T2D susceptible gene. PPARG γ is another relevant gene of interest. Though CAPN10 is another important gene but most studies have not proven that it is significantly associated to T2D.

Transcription Factor 7 Like 2 (TCF7L2)

The association between T2D and a number of single nucleotide polymorphism (SNP) in Transcription factor 7 like 2 genes was established in 2006 by Grant and his team when examining locus linked to T2D on chromosomes 10q25. From the research conducted by Grant and his colleagues, TCF7L2 was detected as a unique susceptibility gene for T2D development and its association with microsatellite marker DG10S478 among intron 3 was also reported [25]. TCF7L2 gene has been considered as the strongest T2D susceptible gene. TCF7L2 gene and its association with T2D has been Systematically confirmed in multiple order of genome wide association studies (GWAS) in different ethnic teams and this gene remains the foremost powerfully associated T2D risk gene at this point [26]. TCF7L2 is connected with diminished insulin discharge and β - cell operation. Loos et al., [27] indicated that the diminished insulin discharge can be resolved by a diminished incretion effect.

Peroxisome Proliferators- Activated Receptor Gamma Genes (PPARG γ)

PPARG γ is a nuclear hormone receptor usually expressed in adipose tissue. A form of PPARG γ gene has the potential to decrease insulin response and increase T2D risk by many folds. Nandi et al., [28] stated that PPARG γ is a target of the anti- diabetic insulin sensitivity medicines known as thiazolidinediones. However, the minor Ala- allele in PPARG (Pro12Ala, rs1801282) has been related with lower BMI, increased insulin sensitivity with reduced risk of T2D. Zeggini et al., [29] stated that this association has been established by many recent genome wide association studies for T2D.

Calpain 10 (CAPN10)

Hanis et al., [30] stated that CAPN10 was the primary T2D gene to be discovered by linkage analyses in 1996 when locus on chromosome 2 was associated with T2D. Subsequently, studies have not always proven that this gene is significantly associated with T2D. However, larger meta- analysis have shown that variants in CAPN10 are seemingly to be actually related to T2D [23]. According to Cox et al., [31], CAPN10 can encode on intracellular calcium- dependent cysteine protease expressly.

1.3.1.1 Other T2D susceptibility genes

Some susceptible genes have been linked with T2D development in some studies but are not closely associated to T2D. Some of these genes include; ADBR3, PPARGCIA, ENPPI and others [33]. Due to their biological functions, certain of those genes have been reported as candidate genes. Also, in recent research five new genes region suspected to be associated in T2D were identified by GWAS which include SLC30A8, CDKAL1, CDKN2A, IGF2BP2 and FTO [34]. None of these regions contains previously known obvious candidate genes thereby showing the ability of GWAS to uncover new physiological pathway.

1.3.2 Gene-diet interaction and t2d

Environmental factors such as lifestyle and diet are the major factors affecting the prevalence as well as the development of T2D. The increase in the risk of T2D can be linked to the interaction between dietary factors and genetic variants [35]. In several studies, TCF7L2 genes have showed strong association in the development of T2D and also interact with the diet modifying susceptibility of T2D. The city Diet and cancer study (MDCS) cohort conducted by Hindy et al., [32] showed that top fiber intake improved abstinence plasma aldohexose and hormone levels with lower levels of glycosylated Haemoglobin. Although, the T2D risk in individual carrying the chance factor TCF7L2 rs12255372 or rs7903146 was higher once fiber consumption was high. Another recent study on gene-diet interaction showed that TCF7L2 (rs12573128) influenced insulin sensitivity and IGF2BP2 (RS4402960) influenced abdominal fat. This means that factor-dietary fat influence aldohexose homeostasis-related phenotypes and play a vital role in determining the high risk of polygenic disease related to T2D susceptibleness gene [36].

1.4 Nutrigenetics Approximation to t2d

Over the years, completely different studies have joined diet chiefly dietary fibre, gut microbiota and organic phenomenon to play a role in immune response. Lifestyle plays an important role within the development of T2D. Studies that have investigated the gene-lifestyle interactions in T2D have prompted that biological effects of genetic predisposition could also be fully discarded by healthy lifestyle [37]. Biological process recommendations are applicable for

persons with T2D as a result of several persons with T2D are overweight and hormone resistance. Medical institute ought to emphasize a lot of on fashion changes that end in reduced energy intake and enlarged energy expenditure through physical activities.

In general, nutrients will have an effect on organic phenomenon in several ways such as;

- a. Nutrients directly act as an ion or molecule for transcription factors and alter the organic phenomenon of the genes
- b. Nutrients could also be metabolized by completely different pathway, thereby modifying the concentration of substrates that have an effect on the organic structure of gene
- c. Nutrients will modify signal pathways which can modulate the metabolism of nutrients affecting the organic phenomenon of gene expression. The modifications in gene expression may affect muscle, liver, pancreatic cells and adipose tissue thereby regulate aldohexose physiological condition.

1.5 Nutrigenomics for Management of T2DM

The following are the contributing factor of type 2 diabetes mellitus (T2DM) which includes; heredity, sporogenous, habitat, and particularly selection of food, i.e diet which is a major metabolic disorder [38]. These factors listed above affects the way in which the genetic makeup of a person is expressed in insulin secretions, in the process of insulin responsiveness over the outer material. However, Hyperglycemia and hyperlipidemia are the major contributing factors of T2DM, which is caused by the over Production of ROS (reactive oxygen species) and the receptive nitrogen types (RNS), which then make oxidation pressure [39]. The usual biological absorption of glucose, polypeptide, fat and osmolarity are affected by ROS/ RNS- induced oxidative stress, which is a gateway toward genetic data and inherited uncertainty, biological destruction, swelling and weaken body part outcome [40]. Pancreatic cells are said to possess small endogenous free radical volume, these cause them to be very vulnerable to oxidation [41]. Insufficient insulin production is as a result of surplus ROS secretion in the affected cells. Tangvarasitichai [42] reported that, the combination of ceramide is as a result of lipid and phospholipid reaction,

which occurs in lipemia. These reaction together with surplus nitrogen oxide (NO) display the beginning production of damage insulin and that of cell death. Plant-based products, that contains polyphenols and phenolic compounds have showed corrective interest next to changing physiological procedures of T2DM [43]. Dietary polyphenols and phenolic compounds have showed ability to control the manner in which genetic codes are involved in insulin production. Phosphoenol pyruvate carboxykinase (PECK) that are found in human hepatoma cells, various polyphenolic compounds, threonin proteinkinase 1 (AK1), have shown ability to modulate the expression of insulin receptors [44]. Normal glucose homeostatic function is as a result of the positive outcome of polyphenolic compounds on these pathways with relation to improved insulin sensitivity, reduced lipotoxicity and hepatic glucose output.

1.6 Nutrigenomics as an Intervention for Geriatric Diabetes

Diabetes Atlas, gave a statistic in the year 2019, that the number of persons tolerating diabetes presently is one hundred and ninety in population and it is believed to increase approximately twice in the year 2025. Geriatric diabetes persons are increasing significantly yearly, yet we do not know the right medication and diet to help them. The way out of geriatric diabetes is Nutrigenomics as it examines the transformations brought about on the genes by nutrition and it also considers the convergence of fitness, nutrients and genetic data. Nutrient-dense foods can be a tool in improving the nutritional status of the aged. Furthermore, blood sugar can be reduced through intermittent fasting, while sugar curtailment lengthen lifetime and lower most hereditary susceptible diseases. These also can be used to prevent and reduce cancer [45].

Today, many natural foods used in the production of undiluted components have exhibit the ability to enlongate the lifecycle and reduced the chance of aged related ill health in prototype living organisms by regulating the mentioned food sensing [46].

Quantitative trait nucleotides (QTNs) identification in geriatric diabetic people

Ron and Weller [47], gave an explanation that quantitative traits nucleotides are nucleotide

polymorphism which greatly interact with quantitative trait. Single nucleotide polymorphism (SNP) is the most used example of a QTN that alters the sixth codon of the hemoglobin gene from a glutamic acid to a valine and thereby alters the amino acid so that it causes anaemic diseases. In 1949, Pauling [48] found out that next to successive straight amino acid chain, that is the initial sample of a particular inherited illness that the main aim of the QTNs examination within this geriatric diabetic population is to disclose SNPs that contest with phenolic compounds. The benefits of QTNs to a geriatric diabetic patient are: to help deduce from their genetic makeup the risk of having diabetes later in life. Furthermore, it is of great assistance in distinguishing quantitative traits transcripts (QTTs) and other forms of quantitative traits. Gene expression patterns vary from person to person.

Quantitative traits transcripts (QTT) is the initial step toward customized medication and nutrient [49]. To get a good result, specific samples from many sick persons are collected to conduct quantitative trait transcripts step, and also entire genetic data utterance outlines. For example: intense intestinal adipose and full blood is superior to CD4 + vital fluid units. One can work alongside with produced multi potent starter units (IPSC) and alternately obtained material. An extra accurate and possibly computable proposal to meet the requirements of the quantity of messenger RNA from a tissue that is used in the coming generation of DNA order technique. QTTs can be known when chromosome defining studies of many patients from specific tissues are completed and that between two people only with the same phenotype that is being interrogated are QTTs.

Finally, Nutrigenomics is the revolution in treating geriatric diabetic population. The ultimate potential of these Nutrigenomics depends upon experiments that are carried out on a sizeable number of geriatric diabetic people with known genomic successions and gene methylation designs. To this end, a person can bring in this understanding to forecast the results upon sufferer's analytical class that did not partook in the experiment [50]. The future of Nutrigenomics is when a sufferer can get nutrient and medications that are specific to them.

Table 1. Several T2D susceptibility genes [32]

Gene	Locus	Variant	Estimated RR ¹
TCF7L2	10q25	DG10S478	1-2
PPARG [□]	3p25	Pro12Ala	1-3
CALPN10	2q37	A43G	1-4

RR= relative risk

2. CONCLUSION

This review evaluate the interaction of genes, diet, and environment as a key factor in the development of Diabetes mellitus type 2 (T2D) disorder, Nutrigenomics have helped to understand this interaction. The following are the susceptible genes of T2D which includes: TCFL2, PPARGY ,CAP 10 ,ADBR3, DPARGCIA, and EMPP genes. Further research have to be done on individual with these susceptible genes to have resistant to T2M and also experiments should be done on large number of geriatric diabetic people to know their genetic codes successions and chromosome methylation designs. With these findings a person can forecast if he can be a sufferer in future and way out through diet regimen. When patients can obtain nutrients and medications that are customized to them, then the future of Nutrigenomics is achieved.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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