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REVIEW ARTICLE

Possibility of Dietary Induction of METHFR rs1801133 (SNP) and the Potential Preventive Effect of Curcumin and Metformin in the Presence of Metabolic Syndrome

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Abstract

Obesity, especially the visceral one, insulin resistance, atherogenic dyslipidemia, and hypertension are considered metabolic disorder, but the constellation of at least three of these metabolic disorders can be identified collectively as metabolic syndrome (MetS), The prevalence of this syndrome is mostly driven by the current changes in the social environment, behavior, and lifestyle, which is generally called a sedentary lifestyle since more and more individuals are being diagnosed with it.The main target of this article is the collection of some available known published papers aboutthe evaluation of dietary induction of metabolic syndrome accompanied with MTHFR rs1801133(MTHFR–Ala222Val)Singlenucleotide polymorphism (SNP) and the potential preventive effect of metformin or curcumin in male albino rat with an induced MetS as a novel method using many biochemical, Anthropometrical, and molecular biological tests including the embedding the RFLP technique for identification of the presence of the target SNP and its role both in the induction of this gene polymorphism and its role in MetS treatment.

Keywords: Metabolic syndrome,Curcumin,Metformin,MTHFR gene polymorphism.

Introduction

The key enzyme in folate metabolism process is MTHFR (methylene-tetrahydrofolate reductase) and its gene SNP rs1801133 is highly suspected to stimulate metabolic syndrome[1], it was well-defined that Type 2 diabetes mellitus (T2DM) risk is raised by five times, cardiovascular disease risk is increased by three times, and the chance of acquiring certain types of cancer is also elevated as a result of the presence of metabolic syndrome[2], in this article we tried to collect representative number of the available published papers about this issues in order to evaluate the dietary induction of MTHFR rs1801133 (MTHFR – Ala222Val) Single nucleotide polymorphism (SNP) which will be accompanied with the presence of diet induced metabolic syndrome and the potential preventive effect of metformin or curcumin.

Metabolic disorder and metabolic syndrome

The failureofusing and/or storing energy is the main factor that characterizes metabolic disorders while diabetes is the most popular type of it, metabolic disorders which occur congenitally mainly are a direct result of some defects including SNPs in genes. These changes may lead to a decrease of essential compounds levels, and/or to aggregation of quantities of precursors, which interfere with normal functions. Metabolic disorders(diabetes, impaired glucose tolerance, anddyslipidemia),

frequently linked with visceral adiposity, are well-known pathogenetic factors[3].

Since 1980, there has been a two-fold increase in the prevalence of obesity. As a result, in 2013, more than 1.9 billion adults worldwide were classified as being overweight. Of these, 600 million were classified as being clinically obese. This means that approximately 39% of the adult population being overweight (38% male, 40% female), and 13% being obese (11% male, 15% female), Moreover, in 2014 it was found that there are about 42 million children under 5 years were diagnosed as obese.

The incredible increase in overweight and obesity numbers was linked to many consequences in human health including metabolic phenomena like (insulin resistance - impaired glucose tolerance - Type 2 diabetes (T2D) –steatohepatitis - hyper lipidaemia), several more endocrine conditions (such as accelerated pubertal development and polycystic ovarian disease), cardiovascular illness (hypertension), as well as numerous respiratory symptoms including shortness of breath and obstructive sleep apnea, and psychological issues include poor self-esteem, bullying, and behavioral issues. Additionally, there is strong evidence that those who are overweight have lower levels of education and income, therefore we may conclude that there is a clear link between obesity and higher adult mortality rates and early death[4].

Atherosclerosis and coronary artery disease are both highly correlated with obesity, especially visceral obesity. The existence of insulin resistance, atherogenic dyslipidemia (high triacyl-glycerides, DecreasedHigh Density Lipoprotein (HDL) cholesterol, and raised tiny, dense Low Density Lipoprotein (LDL) particles), hypertension, and an inflammatory/thrombotic state are the main contributors to these disorders, The metabolic syndrome is the aggregate term for various metabolic diseases when they are discovered at the same time (MetS)[5].

Tabl 1. Metabolic syndrome's definition according to Different organizations [6].

MetS Definitions	WHO	EGIR	NCEP:ATPIII	AACE	IDF
Fundamental	High insulin level	Insulin resistance		Impaired glucose tolerance	WC (ethnic and gender specific)
Component	+2 of:	+2 of:	Any 3 of:	+2 of:	+2 of:
Abdominal obesity	WC >37 inches BMI >30 kg/m^2	WC ≥94 cm (M) ≥80 cm (F)	WC >40 inches (M) >35 inches (F)		
Triglycerides	>150 mg dl^{-1} HDL-C: <35 mg dl^{-1} (M) <39 mg dl^{-1} (F)	>2 mmol l^{-1} HDL-C: <1 mg dl^{-1}	≥150 mg dl^{-1} HDL-C: <40 mg dl^{-1} (M) <50 mg dl^{-1} (F)	≥150 mg dl^{-1} HDL-C: <40 mg dl^{-1} (M) <50 mg dl^{-1} (F)	≥150 mg dl^{-1} HDL-C: <40 mg dl^{-1} (M) <50 mg dl^{-1} (F)
Blood pressure	≥ $\frac{140}{90}$ mm Hg	≥ $\frac{140}{90}$ mm Hg or BP medication	≥ $\frac{130}{85}$ mm Hg	≥ $\frac{130}{85}$ mm Hg	≥ $\frac{130}{85}$ mm Hg
Microalbuminuria	>30 mg g^{-1}				
Fasting plasma glucose		≥6.1 mmol l^{-1}	>110 mg dl^{-1}		≥5.6 mmol l^{-1} or T2DM

Many organizations, including the World Health Organization (WHO), have reached a consensus regarding the factors contributing to MetS, but there is disagreement regarding the specific grouping of these factors and the specific threshold points for each factor that defines MetS because there are so many definitions for identifying MetSTable (1), which contributes to both false-positive and false-negative diagnoses[6].

It is difficult to harmonize these conflicting definitions. However, depending on our current and updated understanding of the pathogenesis of obesity, T2D, and related diseases, future criteria for metabolic syndrome may need to consider the role of adipokines, pro-inflammatory cytokines, and other humoral factors related to insulin resistance, diabetes, and cardiovascular diseases.

It was stated that there is a relation between Metabolic syndrome andincreased risk of Cardio Vascular Disease (CVD), Diabetes mellitus type II (DM II), and mortality; it was reported that the relative risks of these conditions are doubled and tripled, respectively[7].

Due to successful past efforts to end many ofinfectious diseases in the world, non-communicable diseases (NCD) became the mainlife-threatening factorformorbidity and mortality in both developed and underdeveloped countries. One of the highest prevalence and threats is metabolic syndrome[8].

Metabolic syndrome as an epidemic and its economic impact worldwide

Changes in social behavior and lifestyle contribute to an increase in MetS diagnoses, making it a serious public health concern[9], which puts a huge financial burden and threats the quality of life of the patients[10].

In 195 countries a global survey about obesity was done in 2015, its results stated that about 604 million adults and 108 million children were diagnosed with obesity,since 1980, the rate of obese peoplehas doubled in 73 countries and elevated in all other countries with indications of increasing of childhood obesity[11],in this survey, it was observed that obesity prevalence was a cross all socio-economic levels so it isn't yet a disease of high or moderate income levels, thisprevalence rate changed from 1.1% in early 1980 to be 3.85% in early 2015, also it was noticed that starting from 1990 till 2015, the rate of mortality related to increasedBody Mass Index (BMI)elevated by 28.3%, it was also reported as the main cause of 120 million disability-adjusted life-years.

The greatest proportion of age-standard BMI-related fatalities and disability-adjusted life years were discovered in Bangladesh, one of the world's poorest nations; in contrast, age-standard BMI-related morbidity and mortality were found to be 37.2 and 43.7% straight in Turkey[8].

Metformin

Metformin has a long history starting from almost 1772 when it was discovered that it has a good impact on lowering diabetes symptoms, this history can be concluded in table (2) which shows the steps that this medication passes[12].

It was discovered that a traditional herbal remedy used in Europe called Galega officinalis (goat's rue) has a significant amount of Metformin (dimethyl biguanide), one of the main guanidine derivatives, which is the main active ingredient of metformin, in 1918, this extract was used to lower blood glucose.

Other derivatives of this active ingredient, guanidine Figure (1), were synthesized in laboratories and used also to lower blood glucose, in the 1920s and 1930s, metformin was used to cure diabetes, but it was discontinued due to its toxicity and the greater accessibility of insulin. In the 1940s, experiments to find a cure for malaria led to the rediscovery of metformin., Metformin gives a good impact on influenza when lowering blood glucose during clinical trials.

Table 2. History of metformin in treatment of type 2 diabetes[12].

Year	Landmark
1772	*Galega officinalis* used to treat symptoms of diabetes (Hill)
1844–1861	Identification and synthesis of guanidine (Strecker)
1878–1879	Synthesis of biguanide (Rathke)
1918	Guanidine lowers blood glucose in animals (Watanabe)
1922	Synthesis of dimethylbiguanide (Werner and Bell)
1926–1928	Galegine and synthalin lower blood glucose in animals and humans
1929	Metformin and other biguanides lower blood glucose in animals (Hesse and Taubmann; Slotta and Tschesche)
1930s	Use of guanidine derivatives to treat diabetes initially grows then declines due to toxicity and also availability of insulin
1944–1947	Guanidine-based antimalarial agent, proguanil (Paludrine), lowers blood glucose in animals
1949–1950	Dimethylbiguanide (flumamine) tested as potential antimalarial agent and used to treat influenza in Philippines. Also found to potentially lower blood glucose (Garcia)
1956	Jan Aron encourages Jean Sterne and Denise Duval to study guanidine-based glucose-lowering agents
1957	Jean Sterne publishes use of metformin to treat diabetes
1957–1959	Phenformin and buformin reported as treatments for diabetes
1958	Metformin introduced to treat diabetes in the UK and other European countries
1958–1964	Sterne and colleagues (especially Azerad) further evaluate metformin in individuals with diabetes
1968	First large prospective comparator trial of metformin (Edinburgh, UK; notably Duncan, Clarke and Campbell)
1977–1980	Phenformin and buformin withdrawn in most countries because of risk of lactic acidosis
1980–1994	Substantial new scientific and clinical evidence (e.g. Hermann, Noel, Wiernsperger and Bailey), strategic input by Lipha pharmaceuticals (e.g. Howlett, Meynaud, Daniel, Goodman) and discussions with the FDA (Reaven, DeFronzo, Bailey, Turner, Garber)
1994–1995	Metformin approved (1994) and introduced (1995) in the USA
1995–1996	Key publications confirm favourable benefit:risk ratio of metformin in management of T2D
1995–2000	Extensive diabetes education programme by Bristol-Myers Squibb (e.g. Cryer)
1998	UKPDS reports long-term metabolic effects of metformin and reduced cardiovascular risk with use
2000–2002	Extended-release formulation and fixed-dose combination drugs with metformin as the primary active ingredient are approved in the USA
2002	Metformin reduced progression of 'prediabetes' (IGT and/or IFG) to T2D in the DPP
2005	The IDF recommends metformin as an initial glucose-lowering pharmacotherapy for T2D. Other guidelines adopt metformin as an initial glucose-lowering agent
2008	UKPDS follow-up: continued reduction of cardiovascular risk with use of metformin (Holman)
2011	Metformin included in WHO's essential medicines list

In 1957 the French physician, Jean Sterne, reported that metformin can reduce blood glucose levels, however, metformin faced limited attention due to its lower impact if compared with other antihyperglycemic biguanides like buformin and phenformin, which were totally withdrawn from the market due to high risk of lactic acidosis that was appeared in patients in the late 1970s[12].

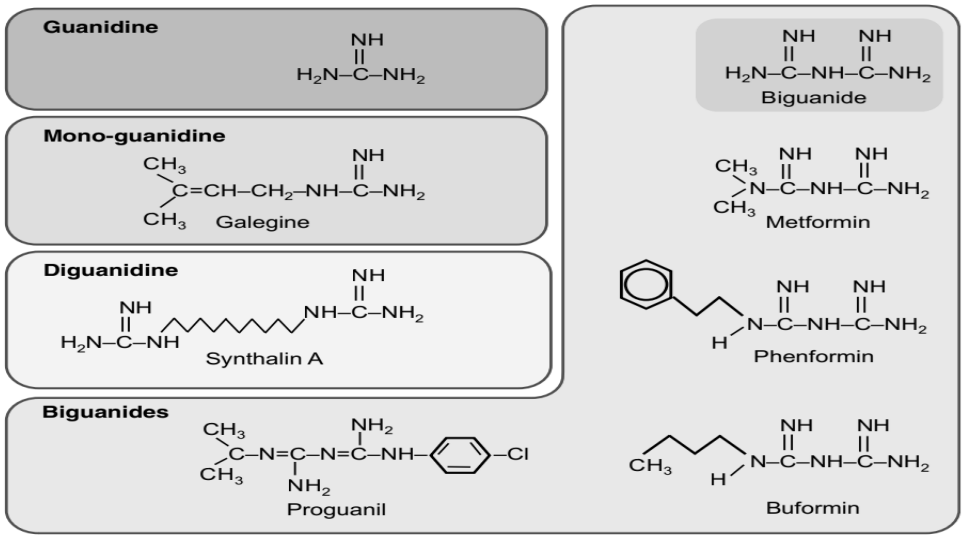

Figure 1. The chemical structure of guanidines[12].

Due to Other guanidine derivatives' bad reputation, Metformin has faced the same destination for a while, but after intensive clinical examination and studies, in 1995, metformin was first made available in the USA. The UK Prospective Diabetes Study (UKPDS) confirmed the long-term cardiovascular benefits of metformin in 1998, giving a fresh justification to certify that metformin become the initial medication to control hyperglycemia in type 2 diabetes[12].

Angiotensin II inhibitor drugs are a significant factor in diabetic nephropathy (DN) prevention. Additionally, metformin, an aminoguanidine derivative hypoglycemic medication, is used by a wide spectrum of consumers to control type II diabetes. Troglitazone and rosiglitazone are insulin sensitizers that effectively lower microalbuminuria independent glycemia. Metformin has been shown in several trials to lower insulin levels, increase insulin sensitivity, and manage hyperglycemia[13].

For most patients with type 2 diabetes up to this point, metformin has been the drug of choice. Metformin has a considerable advantage over all other options because of its high safety evidence and affordable price. Adverse effects are prevalent but may be avoided by meticulous dose titration, ongoing patient relationships, and usage of extended-release formulations. Metformin is the primary medication used to treat hyperglycemia in type 2 diabetes at the moment since it improves glycemic control without increasing weight or hypoglycemia[13].

Currently, Metformin is the main drug for treating type 2 diabetes in most patients. Although adverse reactions are frequent, they can be avoided by careful dosage titration, ongoing communication with patients, and the use of extended-release formulations. Metformin has a major economic and safety benefit over all other options. Metformin is now the major medication used to treat type 2 diabetes hyperglycemia because it improves glycemic control without causing hypoglycemia or weight gain[14].

No safety concerns exist while using metformin for the primary problem with metformin use, which manifests in metformin overdoses, is lactic acidosis caused by an increase in lactic acid, according to more than fifty years of clinical experience and study data. Patients with risk factors for lactic

acidosis, such as hepatic impairment, heart failure, and chronic kidney disease, are not advised to take Metformin because these symptoms were only occasionally noticed in a very small percentage of patients with severe liver, heart, or kidney dysfunction (CKD)[14].

Metformin decreases both basal and postprandial blood glucose levels, which mostly improves glucose tolerance in people with type II diabetes. By enhancing peripheral glucose uptake and utilization, metformin lowers hepatic glucose, decreases intestinal glucose absorption, and improves insulin sensitivity, one of the key benefits of metformin is that, unlike sulfonylureas, it does not cause hypoglycemia in either normal type II diabetic patients or individuals with type 1 diabetes. These results go with a different pharmacologic mechanism that varies from all other forms of antihyperglycemic medicines. Moreover, taking metformin reduces the insulin response throughout the day as well as fasting insulin blood test results, stabilizing insulin secretion[14], so metformin is highly recommended to be used as a natural treatment of Metabolic syndrome and its consequences starting from diabetes type II followed by obesity specially the visceral type which will reduce most of metabolic syndrome risks.

Turmeric and Curcumin

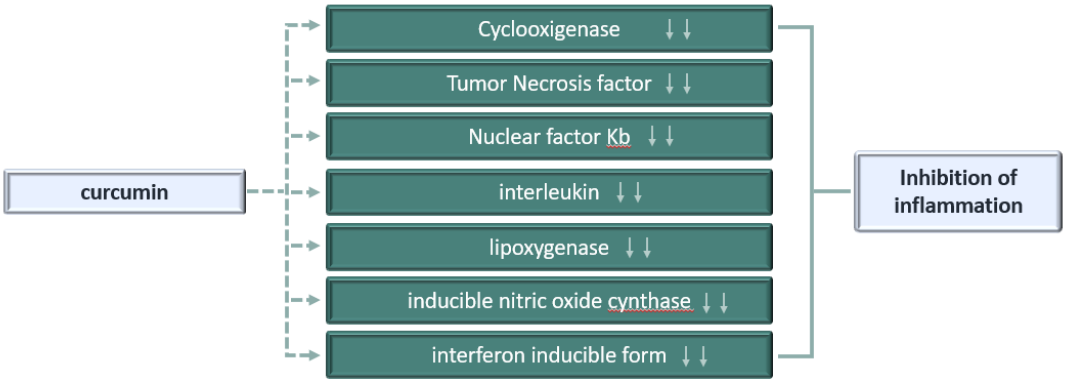

Figure 2.Curcumin's role as anti-inflammatory through inhibition of various genetic pathways[15]

Turmeric (Curcuma longa L),The golden yellow spice, belongs to the Zingiberaceae family[16]. Due to its enhancement of flavor, color, and medicinal capabilities, turmeric is a traditional medicinal herb that has been and is still utilized extensively in local cuisine [17]It has no toxic effects with oral administration[18].

Curcumin or diferuloylmethane (chemical name of curcumin) [19]is the main active component, yellow molecules [20] withphenolic, anti-inflammatory, antioxidant, antidiabetic,[21]antiviral, antibacterial, antifungal[22], and anticancer properties[20], Piperine is an example of many other components, can increase curcumin's bioavailability(Figure 2).

Numerous health benefits of the natural compound curcumin have been seen in diabetic mice, including its impact

on blood sugar and cholesterol levels. Since diabetes is linked to altered lipid and glucose metabolism, the improvement of lipid profiles and glucose management may be responsible for, at least in part, the positive effects of curcumin in the treatment of diabetes. Additionally, studies have shown that curcumin can cause obese rodents to lose weight. Together, we think that curcumin's anti-diabetic benefits result from an increase in fatty acid oxidation, particularly in skeletal muscle[23].

Due to its ability to regulate biological processes, curcumin also demonstrates a crucial function in defending the body against various illnesses. Its ability to scavenge reactive oxygen species (ROS) plays a role in the prevention of numerous pathogeneses. In addition, its capacity to prevent the regulated beginning of styrene oxidation contributes to its antioxidant action, which enables it to prevent DNA damage and lipid peroxidation caused by free radicals[15].

Numerous researchers stated curcumin's biological and pharmacological benefits, which include anti-rheumatic, hypoglycemic, immunomodulatory, hepato-protective, anti-microbial, cardio-protective, anti-neoplastic, antioxidant, anti-inflammatory, and nephroprotective properties[24].

One of the main contributors to lipid metabolism is curcumin, which boosts the activity of lipid mobilization enzymes and suppresses the expression of transcription factors, especially those that are important for hepatic lipogeneses, such as acyl-CoA cholesterol acyltransferase (ACAT) and carnitine palmitoyl transferase 1. (CPT1)[23]. Additionally, curcumin has been reported to have anti-hyperglycemic and anti-hyperlipidemic properties, and this has been confirmed by a study using streptozotocin (STZ) to induce diabetes in rats after curcumin dosage. Curcumin is related to the pathological fat buildup in the liver via the up-regulation of PPAR- through AMPK activation. Separate therapies using both insulin and curcumin were also shown to lower blood sugar, enhance lipid profiles, and raise levels of liver antioxidants[25].

It was stated that curcumin administration reduced hyperglycemia and vascular inflammation in STZ-induced diabetic rats by inhibiting MCP-1, IL-6, HbA1c, TNF, and lipid peroxidation[26].According to a different study, curcumin can increase insulin sensitivity by lowering blood sugar levels and dyslipidemia in high-fat-fed rats[24], so Curcumin is highly recommended to be a natural treatment for metabolic syndrome and reduces its risks.

PCR- RFLP technique

The polymorphism of restriction fragment length Cleaved amplified polymorphic sequence, or PCR-RFLP, was developed by Botstein et al[27]in 1980. In this method, a special restriction enzyme (RE), also known as the recognition site, is added to the PCR amplicon, which causes the restriction enzyme(RE) to cut the DNA in a highly precise restriction site where a specific SNP is found, yielding many DNA fragments of various sizes. The digested amplicons are then loaded using an electric field onto a gel. The variously sized bands will slide across the gel at various speeds[28].

Recent studies using PCR-RFLP have revealed reasonable prices and the significant benefit of minimal equipment investment needs. In addition, genotyping may be done by simply observing restriction fragments by gel electrophoresis without the need for additional softwar[29].

The simplicity of PCR-RFLP makes it possible to do it without extensive

molecular biology training, which is its most potent benefit. Although PCR-RFLP is extremely simple to use, it is only limited by the recognition site of the restriction enzyme, except when double digestion is used with another restriction enzyme, disregarding extra sequences. Since the PCR-RFLP method is constrained to a certain restriction enzyme as a result, it is challenging to identify the precise variation when numerous SNPs are being targeted at once. To some extent, this problem can be solved by mixing more than one restriction enzyme in a reaction mixture[28], Regarding staining process consequences,any commercially available dye will do to stain the digested amplicons in PCR-RFLP. By adding color to the agarose gel before it is polymerized, it would be easier to accomplish[28].

Two procedures that take time to complete a sample are in vitro amplicon digestion with RE and electrophoresis. Depending on the type of RE being utilized, different incubation durations for digestion with REs are necessary. Although most enzymes require an incubation period of 60 minutes to digest their target recognition sequences, other enzymes, such as HinfI only require a 30-minute incubation period, Both agarose gel electrophoresis and very sensitive polyacrylamide gels may be used for RFLP, and the resulting implicated fragments can be found utilizing highly sensitive silver-staining kits[29].

So briefly PCR -RFLP technique can easily identify the presence of SNPs according to detected DNA fragments that can be seen in agarose gel, as the presence of a certain SNP leads to cleave the DNA with the help of the specific restriction enzyme, which could be easily detected using Agarose gel electrophoresis.

Methylene-tetrahydrofolate reductase (MTHFR)

The enzyme MTHFR, also known as methylene-tetrahydrofolate reductase, is essential for the metabolism of folate. It controls methylation, a crucial mechanism for posttranslational changes and epigenetic control, as well as methionine synthesis, which entails the detoxification of homocysteine linked to increased oxidative stress. It also regulates the proportional use of one-carbon units in the synthesis of nucleic acids[1].

The most common and potentially helpful polymorphism, rs1801133 (MTHFR - Ala222Val), has been extensively researched in type 2 diabetes, but less is known about it in MetS, or non-alcoholic fatty liver disease (NAFLD), and it has been linked to atherosclerotic cardiovascular disease, which has contradictory results [30-32]

Mostly in Asians and less in Caucasians, Rs1801133 is associated with elevated homocysteine levels and has been described inconclusively in relation toMetS components and other prevalent illnesses (such as Alzheimer's disease, and depression)[31].

Gene polymorphism

It is noteworthy that the biological consequences of caloric intake are closely related to epigenetic processes. It has been asserted that the interplay between environmental stimuli and intracellular genetic material is what primarily causes these changes in epigenetics[31], In conclusion the human genome comprises more than 3 billion base pairs, which are present in every cell in the human body that has a nucleus, even if genetic diversity is limited to between 0.1% and 0.4%. Between any two humans in the world, this genome, which has remained unharmed over evolution, is shared by at least 99.5%.

Gene polymorphism or mutation may be the cause of this DNA variation. Mutations lead to polymorphisms. Any

variation that results in a disease is referred to as a mutation, especially if it occurs less frequently than 1% of the time,A change in nucleotide type, an insertion or deletion, or a rearrangement of nucleotides can all result in a mutation[34].

Genetic polymorphisms can result from both internal and external factors, such as radiation or viruses. Genetic mutation is a term sometimes used to describe a change in DNA sequence between individuals that have been linked to a disease. Instead of "polymorphism," changes in DNA/sequence that have been demonstrated to be brought about by outside factors are more often referred to as "mutations"[34].

Single nucleotide polymorphisms (SNPs) and DNA sequence polymorphism analysis may give a comprehensive understanding of the evolutionary importance of DNA polymorphisms as well as the selection and demographic forces affecting populations and species. Mutations lead to polymorphisms. Nucleotide changes from one type to another, insertions or deletions, or nucleotide rearrangements can all result in mutations[34].

Once formed, a polymorphism may be passed down from parent to kid just like any other DNA sequence. Outside of genes, the vast portion of DNA that does not code for proteins contains polymorphisms.

Since a mutation in DNA sequences that code for proteins may have negative effects on the person who bears it, regions of the genome that do not code for proteins are likely to have more polymorphisms. Synonymous polymorphisms are thought to be neutral in nature since they have no effect on the organism and do not alter the amino acid content of the protein that is generated. This is also known as a quiet mutation[34].

An altered amino acid is the outcome of a nonsynonymous substitution. A missense mutation alters the codon, which modifies the protein. A misplaced termination codon is the outcome of a nonsense mutation. Nonsynonymous codon alterations are the consequence of 50% of all coding sequence SNPs[34].

It was clearly stated that metabolic syndrome has a relation with gene polymorphism induction, choosing MTHFR and its most popular SNP rs1801133 (MTHFR – Ala222Val) just to assess this relation through using many biochemical (fasting blood glucose, Insulin, HOMA-IR, Lipid profile), Anthropometrical (weight, Length, BodyMass Index) and molecular biological tests, exploring the most available published articles in this context to evaluate this relationship, especially in the presence of both curcumin and metformin as a natural source of treatment of metabolic syndrome[1].

Interleukin-1 β

Pro-inflammatory cytokines, which mainly include IL1β, IL6 and many others, they are all known to be elevated in case of obesity and inflammation so it is common to be identified in an elevated ratios in metabolic syndrome[35]also in obese and T2DM patients, there is a noticeable increase in white blood cell counts, plasma levels of clotting factors like fibrinogen and plasminogen activator inhibitor 1 (PAI1), acute-phase proteins like serum amyloid A (SAA) and C-reactive protein (CRP), pro-inflammatory cytokines like tumor necrosis factor (TNF)-a, interleukin (IL)-1 β, and IL-6, and chemokines[36, 37].

Interleukins, a class of cytokines that mediates inflammation and regulates immunity, were given this name because it was once believed that they mediated

communication between white blood cells[38].

As its name implies, interleukin (IL)-1 was one of the first cytokines to be identified. Many paths led to the identification of the molecules that are now known as IL-1. The effort to identify the transferable sterile factor that induces fever led to the purification of the protein that is now known as IL-1 (endogenous pyrogen activity)[39].

IL-1 β, which initiates a self-amplifying cytokine network, is one of the main pro-inflammatory cytokines produced by macrophages and is anticipated to have a substantial role in the pathogenesis of type 2 diabetes (T2DM). It communicates via the IL-1 receptor-I, which encourages NF-kB pathway activation and the production of additional inflammatory mediators including TNFa and IL-1 β[40].

Two signals are necessary for IL-1 β production regulation. IL1b is initially activated by a pro-inflammatory signal, which causes the cell to collect latent pro-IL-1 β. The inflammasome is brought on by the second signal, a massive cytoplasmic multiprotein complex, to release caspase-1, converting the precursor of IL-1 β from inactive to active and mature[41].

The primary and most important elements of the innate immune response are the inflammasomes, which may recognize both endogenous chemicals and microbial products (pathogen-associated molecular patterns, or PAMPs), as well as danger-associated molecular patterns, or DAMPs[41].

Interleukin-10

On the development and stability of atherosclerotic lesions, it has a preventive effect. Additionally, following human myocardial ischemia/reperfusion damage, it is released into the plasma, perhaps by lymphocytes entering the myocardium, and may inhibit myocardial macrophage activity. The production of proinflammatory cytokines is significantly inhibited by IL-10, which also decreases the involvement of macrophages[42].

The spleen is one of the organs that produce interleukin-10 (IL-10), which has a variety of anti-inflammatory effects. In macrophages, it also controls insulin sensitivity, cholesterol absorption, and efflux. It inhibits IK activity or induces tyrosine phosphorylation of STAT-3 to have immunosuppressive effects by activating the JAK/STAT system via the IL-10 receptor. According to recent research, the spleen's marginal zone-activated B cells, which release high levels of IL-10, have a significant suppressive effect on the harmful immunological responses brought on by obesity[43].

INFKB p65

The fact that obese persons have chronic inflammation is widely established. The NF-B signaling pathway may be activated by the increase of inflammatory mediators in obese people[44].

Increased macrophage infiltration altered cytokine production, and activation of the inflammatory signaling system in adipose tissue are all indications of insulin resistance and obesity, respectively, this illustrates why these obese individuals have higher levels of pro-inflammatorycytokine expression in their adipose tissue and peripheral blood mononuclear cells (PBMC)[45].

Simply put, inflammation is defined as an increase in NF-kB (p50/p65) in the nucleus and a reduction in the inhibitory molecule of NF-kB (IkB-) and/or IkB- at the cellular level, this pleiotropic transcription factor NF-kB, which is activated by reactive oxygen species and

regulates the creation of several cytokines, chemokines, cell adhesion molecules, immunoreceptors, and inflammatory enzymes, is inhibited by antioxidants (ROS)[45].

The NF-B signaling system, whose different components interact and regulate one another, is regarded to be one of the most dynamic protein interaction networks. Only Rel A/p65, C-rel, and RelB include the transactivation domain (TAD), which is essential for transcriptional activity. Each NF-B translational monomer that operates as a homo- or heterodimer has the conserved amino-terminal dimerizing Rel homology domain (RHD)[46].

When homodimerized with a transactivating Rel subunit, the monomers p50 or p52 with a transactivation domain (TAD) defect can stimulate transcription; nevertheless, when monomerized alone, they behave as trans-repressors, the transactivation of target genes for several activities, including cellular proliferation, inflammatory cytokines, chemokines, and mediators of apoptosis, is sufficiently raised even if the increased activation of p65 in response to a variety of stimuli is momentary[46].

Glut 2

In cells throughout all spheres of life, the ability of GLUT 2 to transport hexoses across plasma membranes serves as a signal for the first and rate-determining stage of energy metabolism. In humans, the 14 glucose transporters (GLUTs) from the SLC2 gene family mediate and aid the diffusion of sugar along a concentration gradient[47].

Although GLUTs have fairly similar sequences, they vary in their preferred substrates and binding affinities[47], satisfying the complex, tissue-specific hexose uptake requirements. GLUTs are expressed, localized, or function improperly in several diseases, including cancer[48].

The SLC2A gene family member GLUT2, which has a high Vmax and Km for glucose, can efficiently handle high sugar concentrations[49], The primary GLUT isoform in the liver is GLUT2, which is also found in the gut, pancreatic beta-cells, kidney, and central nervous system. In these and many other tissue organs, it facilitates the transportation of glucose[50].

Glut 4

GLUT4 glucose transporter is crucial for both the removal of glucose from the bloodstream and the control of whole-body glucose homeostasis it is one of the 13 sugar transporter proteins (GLUT1-GLUT12 and HMIT) encoded in the human genome.Adipose and skeletal muscle both express a lot of GLUT4, but both tissues additionally express a specific subset of the other transporters. For example, in response to insulin and other stimuli, GLUT4 has a special property that allows it to be swiftly redistributed to the plasma membrane when it is not active, whereas GLUT1, GLUT5, and GLUT12 may all significantly contribute to the absorption of sugar in skeletal muscle[51].

PPAR γ

The nuclear hormone receptor superfamily includes ligand-activated transcription factors known as peroxisome proliferator-activated receptors. Three isotypes of the PPAR subfamily exist PPAR- (NR1C1), PPAR-/ (NR1C2), and PPAR- (NR1C3). De novo lipogenesis, fatty acid intake, oxidation, storage, and export, cell proliferation, inflammation, and vascular tissue function are just a few of the processes that PPARs significantly contribute to the control[52].

Two different PPAR-splice variants were produced from cloning, PPAR-

1, and PPAR-2. both are nuclear receptors with a relationwith controlling adipocyte growth and maybe lipid metabolism, which raises the possibility that they have a significant role in regulating fat storage,the NH2 terminus is the only and main difference between these two variants of PPAR- 2, which has an extra 30 amino acids. It was shown that decreased PPAR- activity results in adipocytes differentiating more slowly, which boosts insulin sensitivity and decreases body fat index (BMI)[53].

Conclusion

We reached the consensus that the presence of MTHFR rs1801133 (MTHFR – Ala222Val) SNP raises the opportunity of occurring metabolic syndrome, but it also raises the possibility of curing and the efficacy of treatment in some cases, this gives us new hope to help people to get rid of this burden using natural extracts, surly with a new and healthier lifestyle.

Conflict of Interest

The authors have no conflict to declare.

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الملخص العربى

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الإختلال الأيضي يتضمن مجموعة من الأمراض من أهمها السمنة، وعلى الأخص تلك التي تتركز في منطقة الاحشاء، ومقاومة الأنسولين وتصلب الشرايين وإرتفاع الضغط, لكن تواجد تلك الأمراض في نفس الوقت درج على تسميته متزامنة الأيض . يحدث الإنتشار السريع لهذه المتزامنة نتيجة التغيرات في السلوك الإجتماعي للبشر والذي أطلق عليه أسلوب الحياة المستقر أو النمطي.نتطرق فى البحث المرجعى الدراسة الأبحاث العلمية المتاحة التي تناولت كيفية الحدوث الطبيعي لمرض متلازمة التمثيل الغذائي، بوجبات دسمة مليئة بالدهون، والتركيز علي دور ما يتناوله الإنسان في إحداث تعدداتجينية حيث تم التركيز علي MTHFR وخاصة تعدد الشكل الجيني SNP وخاصة ذلك المعروف بإسم (MTHFR – rs1801133 Ala222Val)، بإستخدام تقنية RFLP والتركيز علي دور كل من الكركم و الميتفورمين كعلاج مقترح.