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The Role of Polyamines in Metabolic Syndrome

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Abstract
Metabolic syndrome has become a major health hazard worldwide, due to an increased consumption of fast food along with other unhealthy eating habits, decrease in physical activities and major lifestyle changes as a result of modernization. Metabolic syndrome is a non-communicable disease resulting in complications like type 2 diabetes, coronary diseases, stroke etc. The polyamines putrescine, spermidine, and spermine are naturally occurring cationic molecules essential for various cellular functions. Dysregulated polyamine circulation and metabolism have been linked to several conditions including cancer, type 2 diabetes mellitus, adipogenesis, altered lipid or glucose metabolism, chronic inflammation, etc. Several studies regarding the role of polyamines in metabolic syndrome in various models have been conducted, and the outcomes suggest a positive correlation in the prognosis of metabolic syndrome. This review provides a comprehensive discussion of metabolic syndrome, its prevalence in India and worldwide, factors causing the syndrome, and the role of polyamines in the pathogenesis of various complications of metabolic syndrome.

Keywords: Metabolic Syndrome (MetS), Obesity, Polyamines, Type 2 Diabetes Mellitus (T2D)

1. Introduction
Metabolic Syndrome (MetS) is a trait that highlights the possible increased risk of many diseases. WHO, in 1999, defined MetS as a pathological condition with abdominal obesity, insulin resistance, hypertension and hyperlipidemia. It is also known in the literature as insulin resistance syndrome, syndrome X, pluri-metabolic syndrome, Raeven's syndrome and deadly quartet[1,2]. The syndrome is correlated with several risk factors of separate origin, like obesity, dyslipidaemia, hypertension and hyperglycaemia. It also carries the risk of placing the affected person in prothrombic and proinflammatory states[3]. Factors like physical inactivity, aging and hormonal imbalance also contribute to MetS[4]. Persons with metabolic diseases have a 2-fold increased risk for cardiovascular diseases and a 5-fold increased risk for Diabetes Mellitus 2[5].

2. Prevalence of MetS
Various studies have been conducted around the globe and certain trends relating prevalence of MetS to age, sex, lifestyle, ethnicity, socio-economic background and presence of obesity have been observed. As obesity and type 2 diabetes are a few of the major factors indicating risk and/or presence of MetS, various studies have been conducted by the health monitoring agencies, such as National Youth Fitness Survey (NHNES), Centre for Disease Control and Prevention (CDC), etc., focusing on it. The studies have also confirmed that prevalence of MetS and MetS-related conditions increase with age and certain ethnic groups have higher risk than others. A study published in the *American Journal of Medical Sciences* reported that about 44% of the US population above the age of 20 years was diagnosed with at least two major health abnormalities related to MetS[6].

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Reports suggest that females are at a higher risk in developing MetS conditions than the male. Further, obese females with more deposition of body fat above the abdomen are at a higher risk for insulin-resistance, hyperinsulinemia, glucose-intolerance, and dyslipidaemia than other females[2]. A global survey on obesity in 2015 revealed 604 million adults and 108 million children, residing in 195 countries, as obese. The same agency reported that in a span of about three decades, prevalence of obesity doubled in 73 countries and increased in most of the other countries that were part of this survey[7].

In 2017, CDC published a data according to which 12.2% of the adult population (more than or equal to 18 years of age) in the United States were diagnosed with type 2 diabetes. The percentage of individuals with type 2 diabetes increased to 25.2% for the study group that was equal to or more than 65 year old[8]. Another study focused on the study taking into account the ethnicity of the subjects reported that type 2 diabetes was more common among the Asian Americans than rest of the non-Hispanic white population. The study reported that prevalence of type 2 diabetes was highest among the American Indians (15%)[9]. Prevalence of MetS and/or prediabetic condition is almost 3-folds more than the prevalence of type 2 diabetes[8] (https://www.cdc.gov/diabetes/data/statistics-report/index.html). The global scenario in terms of prevalence of MetS can be summarized by stating that it affects almost 30% of the Indians, 34.7% of Americans, 40% of the total population from middle-east countries, and 15.5% of Chinese (predicted)[10–13] (Figures 1 and 2).

3. Obesity and MetS

WHO defined overweight and obesity as excess of accumulation of fat that presents a risk to health. Body Mass Index (BMI) is considered to be a crude population measure for obesity. A person with a BMI of 25–29.9 is considered overweight and a BMI of 30 and above is considered obese. Obesity is an altered state of adipogenesis. Adipose tissue secretes a huge array of chemocytokines known as adipokines and in obesity these adipokines are altered, e.g., adiponectin is anti-inflammatory whereas leptin, TNF-α, IL-6, IL-34 and resistin are pro-inflammatory. Dysregulation of the pro-inflammatory and anti-inflammatory adipokines results in various metabolic anomalies leading to diabetes, insulin resistance, hypertension, lipid disorders, etc., that are related to MetS[14–16].

Adipocytokines like adiponectin and leptin have been investigated to comprehend the pathophysiology

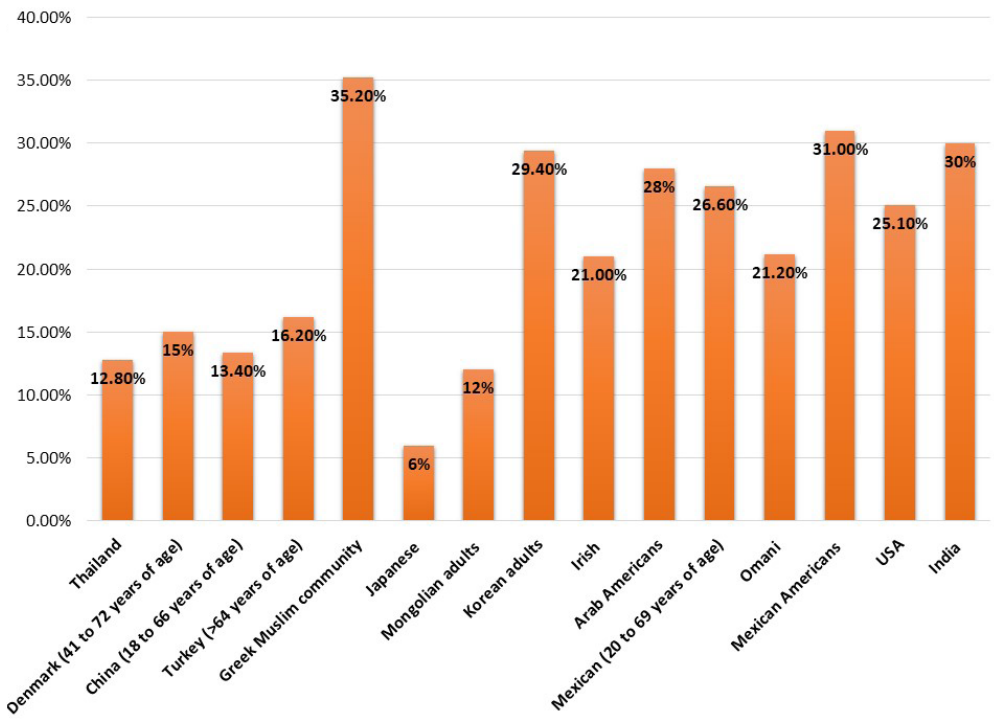

Figure 1. Data on prevalence of MetS compiled from various sources[10–13].

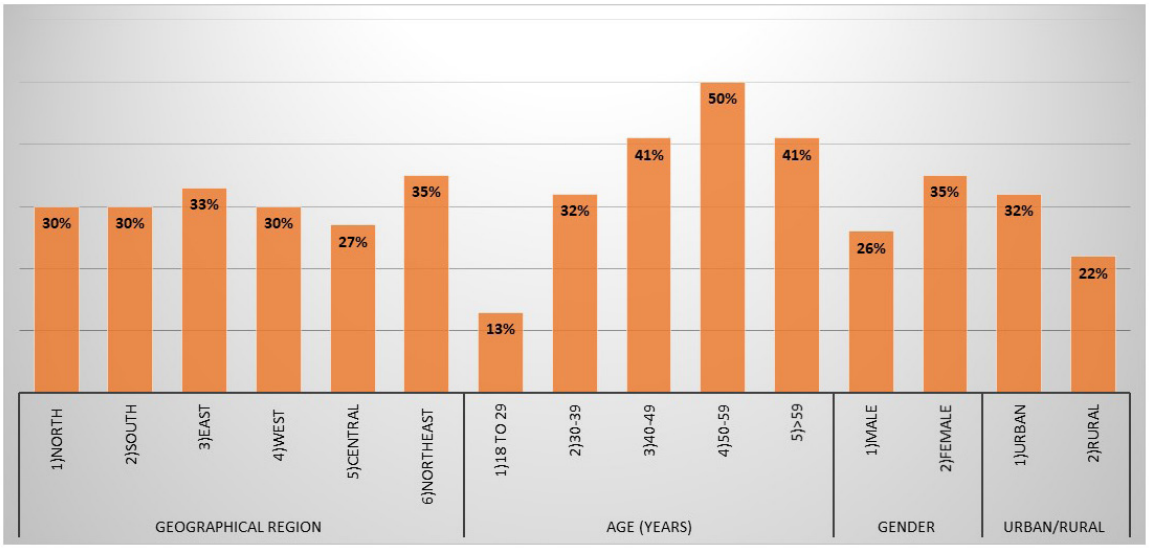

Figure 2. Data on prevalence of MetS in India among groups categorized based on the graphical location they belong to, age, gender or lifestyle (urban or rural) that they follow[11].

of MetS as leptin resistance, hyperliptinemia and hypoadiponectinemia are associated with MetS, diabetes, hypertension, dyslipidemia, etc.,[17,18]. Adiponectin level is reported to be lower in obese and T2DM conditions whereas the circulating levels of leptin and resistin increase by more than two-folds in patients with T2DM[19].

Atherogenic dyslipidemia, high blood pressure and elevated blood glucose level are recognized risk factors for MetS[4]. Deposition of triglycerides (non-alcoholic fatty liver disease) also disrupts the glucose and insulin metabolism and it is related to metabolic dysfunctions and cardiovascular risk factors[20]. As per the International Diabetes Federation (IDF), 8.8% of the global adult population already had diabetes in 2017[21]. As per the same report, 'India is the epicentre of diabetes mellitus and it was found that in 2017 India had the second-largest populace of 73 million diabetic patients, after China and the figure is expected to be just double, 134 millions, by 2045' as within a span of 10 years, prevalence of type 2 diabetes increased from 7.1% (2009) to 8.9% (2019). Indian Council of Medical Research (ICMR-INDIAB) conducted a study to investigate the prevalence of urban and rural Indian population, and found that 13.9% of subjects had hypercholesterolemia, 29.5% had hypertriglyceridemia, 72.3% had low HDL-C, 11.8% had high LDL-C, and 79% had abnormalities in one of the lipid parameters[22]. Results from the ICMR–INDIAB population-based cross-sectional study on the prevalence of diabetes and prediabetes in several Indian states showed that the prevalence varied from approximately 4% in Bihar to 10% in the northern state of Punjab and was even higher in urban areas than rural areas[23]. Upon combining findings of several studies, Gupta *et al.*, in their review, concluded that prevalence of hypercholesterolemia among the urban population varied from 25% to 30% whereas for the rural population of India the prevalence ranged at 15–20% (Figures 3, 4)[24].

4. Polyamines and MetS

Polyamines are a class of naturally occurring polycationic compounds. They participate in several cellular functions like cell proliferation, apoptosis and differentiation. They regulate translation by binding and stabilizing the DNA and RNA and by modulating enzyme functions along with its antioxidizing properties[25]. In mammalian cells, putrescine, spermidine and spermine are the predominant polyamines. In the biosynthetic pathway polyamines are produced from the amino acids L-arginine or L-proline via L-ornithine[26]. Putrescine, one of the polyamines, is formed from the decarboxylation of L-ornithine in the presence of ornithine decarboxylase1 (ODC1). Putrescine then gets further converted to spermidine and spermine by the action of spermidine synthase and spermine synthase, respectively[27]. In addition to the above pathway, sometimes in the absence of the ODC1 enzyme, there is

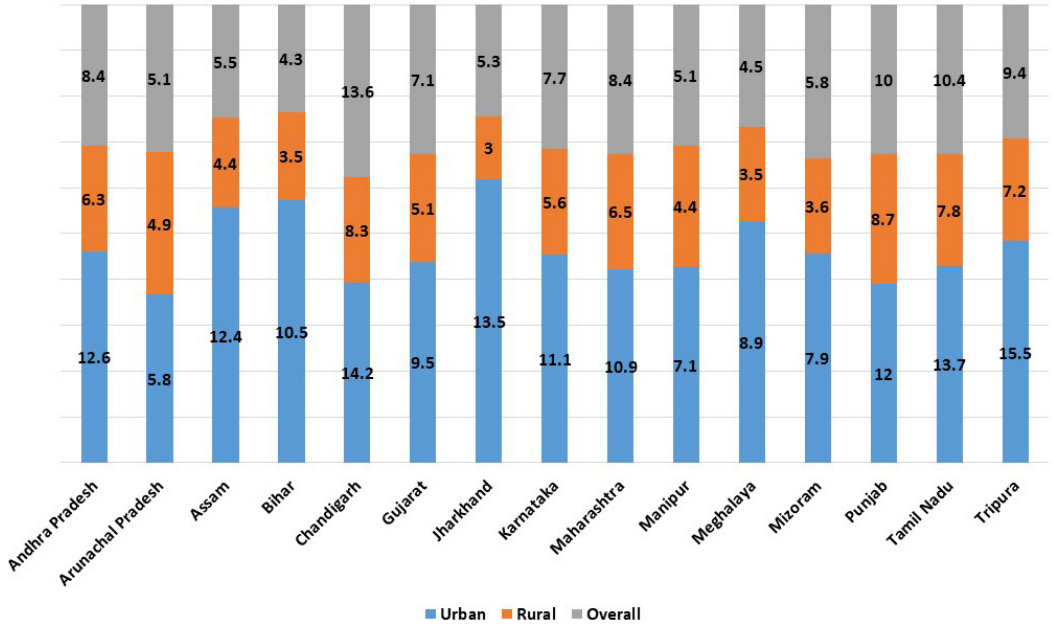

Figure 3. Prevalence of diabetes in various states of India[24].

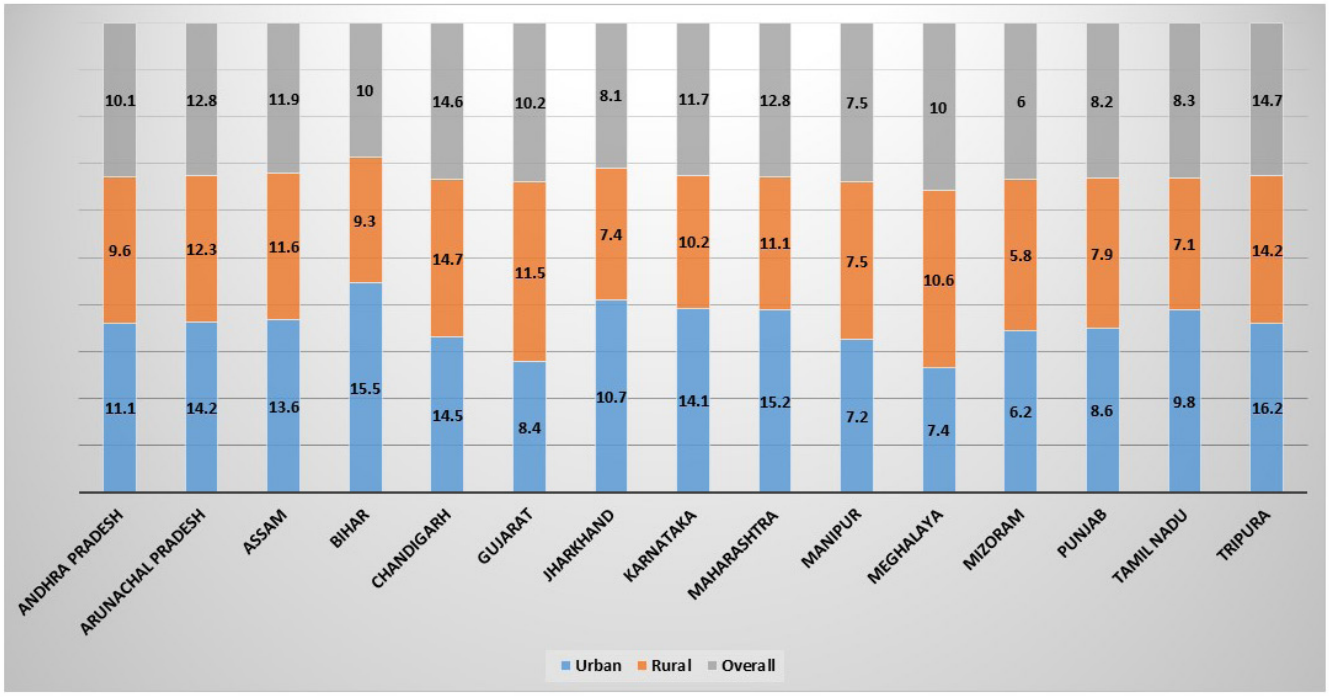

Figure 4. Prevalence of pre-diabetes in various states of India[24].

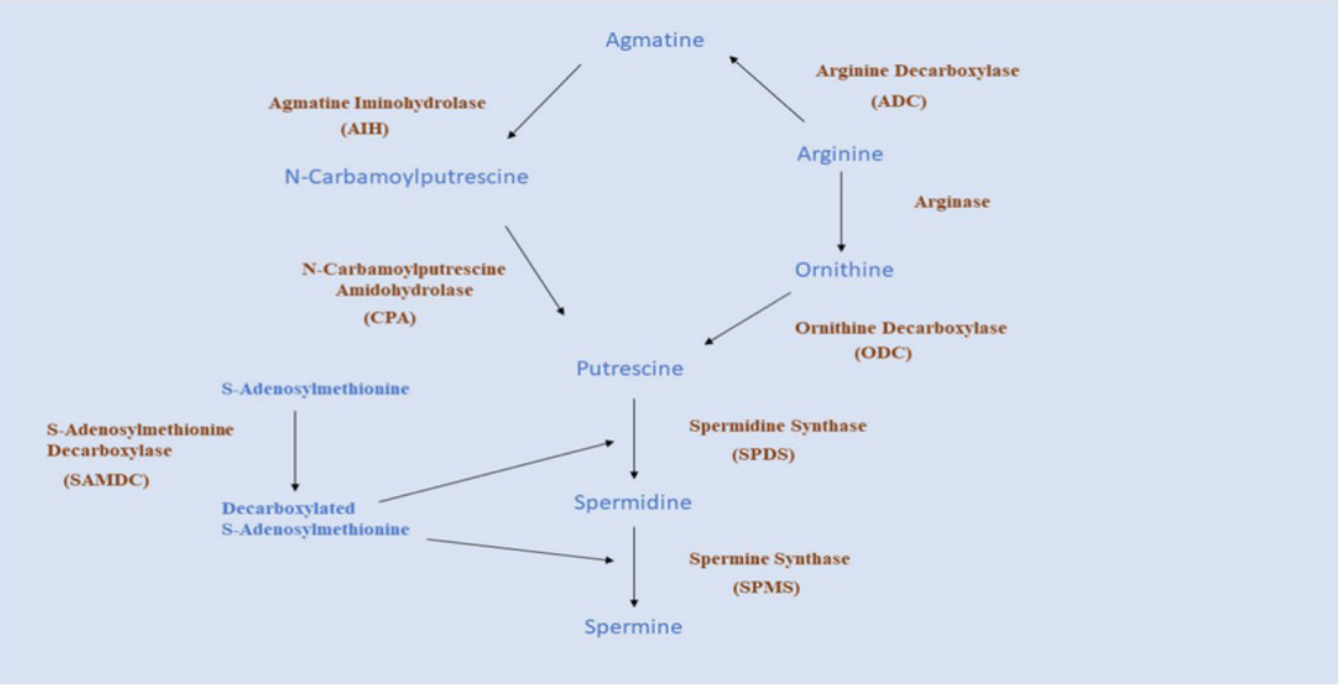

Figure 5. The biological pathway of polyamine metabolism.

a functional compensatory pathway for production of polyamine, through the arginine-agmatine-polyamine pathway (AGMAT) (Figure 5)[28].

Polyamine uptake from the extracellular space, its endogenous biosynthesis, catabolism, urinary excretion, and transport determine the intracellular spermidine content. In mammals, proteins called antizymes and antizyme inhibitors control production as well as uptake of polyamines from the extracellular space[29]. Spermine and spermidine obtained through ingestion are quickly adsorbed and distributed from the intestine without further degradation. Blood polyamine concentration is thus greatly influenced by diet, which is highly diverse in humans. Spermidine is formed from either its precursor putrescine or by spermine degradation. Acetylation and oxidation reactions mediate spermidine catabolism. Synthesis of spermidine and spermine is regulated by the formation of decarboxylated S-adenosyl methionine (dcSAM) from SAM[25]. Further, polyamine oxidase (PAO), an enzyme which catalyzes the oxidative deamination of spermine and spermidine, contributes to ammonia production[30].

In pancreas, polyamines are located in the islet β cells and are responsible for proinsulin biosynthesis and insulin secretions[31]. Insulin gene expression and protein synthesis have been shown to be affected positively by polyamines[32,33]. Polyamines have been shown to be crucial for pancreatic cell differentiation and organogenesis. Deprivation of polyamines has led to reduced pancreatic β cell mass[34]. Study by Fernandez-Garcia *et al.*, revealed that serum polyamine profile of putrescine in Type 2 Diabetes patients is comparatively higher than in non-diabetic subjects and this could be due to the impaired conversion of putrescine into spermidine by spermidine synthase in T2D condition[35]. Serum levels of polyamines have been shown in the same study to be positively correlated with the serum levels of glycosylated hemoglobin (HbA1c) in T2D patients. Further, another polyamine, agmatine, has been shown to reduce triglyceride, and low and very low density lipoprotein cholesterol levels in high fat fed diet induced T2D rats. In the same study it was shown that agmatine might have beneficial effect in managing insulin resistance through decrease in glucose transporter type-2 (GLUT-2), mammalian target of rapamycin (mTOR) and sterol regulatory element-binding protein-1c (SREBP-1c) in liver of T2D rodent model[36]. Recently, it has been shown that agmatine might reduce cognitive decline in T2D mice[34].

Polyamine metabolism has been reported to be dysregulated in MetS[29]. Studies suggest that polyamine metabolism plays a role in MetS via pathways involved in homeostasis of glucose, lipid and energy[37–40]. Putrecine

levels have been reported to be high in childhood cases of obesity[41,42]. Also, adipose tissue of morbidly obese insulin resistant subjects is observed to have an elevated polyamine levels[41,42]. While, most of the studies have focused on circulating levels of polyamines as a whole in their studies, very few focused on levels of individual polyamines in the various conditions. These studies confirmed that spermidine acted as a protective factor against obesity inducing factors[43–45].

Administration of natural polyamines like spermidine through *in vivo* and *in vitro* approaches has been showed to have a beneficial effect in regulating processes like stress, chronic inflammation, dysregulated lipid or glucose metabolism, etc. Polyamine metabolism is directly linked with adipogenesis. Increased polyamine levels implement the involvement of adipose tissues in obesity[37,38]. A study in 3T3-L1 preadipocytes showed that spermidine and spermine are required for adipocyte differentiation by regulating at the transcriptional level in the process of adipogenesis[46]. Contrary to these results, in the high fat fed mice model, daily administration of high dose of polyamines has shown to be an effective strategy for the improvement of glycemic conditions[43]. Epidemiological studies conducted in humans showed that high consumption of dietary spermidine is associated with reduced cardiovascular events and decreased mortality[35]. In rat adipocytes, spermine enhances glucose transport and its metabolism into triacylglycerol and to increase insulin and insulin receptor binding[47]. Several recent studies suggest that spermine, together with insulin, when released into the circulation, modulates glucose homeostasis by its endogenous insulin sensitizer effect. Earlier report showed that spermidine supplementation resulted in the reduction of body weight followed by increased glucose tolerance, insulin sensitivity and decreased hepatic steatosis in high-fat diet-induced obese mice[48]. Exogenous spermine treatment brought about significant decrease in body weight, lowering of fasting glucose levels as well as improvement in glucose tolerance in diet-induced obese mice models. Experiments in diabetic rat models concluded that spermine administration improved the lipid profile by reducing the formation of advanced glycation end-products in in-vivo conditions[29]. A study by Luis Ocaña-Wilhelm *et al.*, first described the influence of sleeve gastronomy on blood level of polyamine metabolites in obese individuals and it was also demonstrated that the polyamine metabolome gets affected by the Bariatric Surgery (BS) in morbidly obese individuals; further the authors showed that patients who had gone through BS displayed a different circulating polyamine profile[49].

Thus, in conclusion, it can be said that metabolic syndrome is a wide range of complications affecting a broad variety of populations due to lifestyle changes. Along with altered inflammatory responses in MetS and obesity, polyamines now have emerged as important biomolecules which undergo alteration in these pathophysiological conditions. Numerous studies support the role of polyamines in both triggering and controlling the disorder and it serves as a prospective field of research owing to the increasing complications as a result of MetS. Polyamines in future might turn out to be an essential biomarker as well as new target for novel drug designing for such conditions and a detailed investigation in this regard is highly pertinent.

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