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Review

Salts and energy balance: A special role for dietary salts in metabolic syndrome

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SUMMARY

Background: Dietary salts sodium (Na^+), potassium (K^+), magnesium ($Mg2^+$), and calcium ($Ca2^+$) are important in metabolic diseases. Yet, we do not have sufficient understanding on the salts global molecular network in these diseases. In this systematic review we have pooled information to identify the general effect of salts on obesity, insulin resistance and hypertension.
Aims: To assess the roles of salts in metabolic disorders by focusing on their individual effect and the network effect among these salts.
Methods: We searched articles in PubMed, EMBASE and Google Scholar. We selected original laboratory research, systematic reviews, clinical trials, observational studies and epidemiological data that focused on dietary salts and followed the preferred reporting items for systematic review in designing the present systematic review.
Results: From the initial search of 2898 studies we selected a total of 199 articles that met our inclusion criteria and data extraction. Alterations in metabolic pathways associated with the sensitivity of sodium, potassium, magnesium and calcium may lead to obesity, hypertension, and insulin resistance. We found that the results of most laboratory research, animal studies and clinical trials are coherent but some research outcome are either inconsistent or inconclusive.
Conclusion: Important of salts in metabolic disorder is evident. In order to assess the effects of dietary salts in metablic diseases, environmental factors, dietary habits, physical activity, and the microbiome, should be considered in any study. Although interest in this area of research continues to grow, the challenge is to integrate the action of these salts in metabolic syndrom.

1. Introduction

Metabolic syndrome is a complex disorder combining obesity, insulin resistance, dyslipidemia, and hypertension. These are also the primary risk factor for diabetes and cardiovascular disease, which are inseparably linked to consumption of fatty foods. According to the World Health Organization, 1.9 billion adults (≥20%) are overweight, of which nearly 600 million are obese. Childhood obesity is also increasing, with more than 41 million overweight children (aged ≤ 5 years) were reported in 2014. It is estimated that 2.8 million adults die annually as a result of being obese or overweight [1] In addition to fatty foods the unbalanced use of dietary salts in our foods can also cause the problem of obesity. Here, we focus on dietary salts, sodium (Na^+), potassium (K^+), magnesium (Mg^{2+}), and calcium (Ca^{2+}) and their role in metabolic disorder. Not only these salts are essential for life but salts also serve as the building blocks of skeleton, and tissues in addition to be a vital

Abbreviations: CaSR, calcium sensor; C/EBPα, CCAAT/enhancer-binding proteins; *C. elegans*, *Caenorhabditis elegans*; KLF, krüppel-like factors; NGM, nutrient growth media; PPARγ, Peroxisome proliferator-activated receptors; ADD1/SREBP, Sterol regulatory element binding proteins; PTH, parathyroid hormone; WT, wildtype.

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component of enzymes, vitamins and hormones. Exactly how dietary salts achieve magnitude of diverse roles in metabolism is largely unexplained, although it may be apparent by their multiple distinct functions. Although our understanding of the regulatory mechanisms and the signaling molecules that are influenced by salts has progressed, we have not yet gained sufficient knowledge to enhance our ability to understand the impact of dietary salts in human physiology. The biology of dietary salts is an interesting but under-investigated field and obviously there is a need for more data.

Wide-range of epidemiological and clinical studies along with genetic studies in animals has identified certain salts with likely roles in metabolic pathway. Dietary Ca^{2+}, for example, is an important element in skeleton formation, blood clotting, contraction and relaxation of muscles, blood pressure and intracellular signaling, whereas K^+ maintains normal fluid and electrolyte balance; supports cell integrity, and muscle contractions. Potassium is a crucial component of biochemical pathways that regulate many cellular activities. Further, K^+ is an important factor in energy metabolism. Variation in K^+ level can contribute to hypertension, insulin resistance, diabetes, and vascular disease. Magnesium is a known activator of the intestinal peptidase activities, it is also involved in the regulation of blood sugar, promotes normal blood pressure, and is a key factor in energy metabolism and protein synthesis [2]. Sodium is considered to be one of the most essential minerals required for the human body. Although some amount of Na^+ is needed to continue normal body activities, the high Na^+ intake is a major factor involving in many serious diseases [3] for instance, high blood pressure.

Combinations of laboratory experiments, suggestive evidence from observational records and clinical studies on human consumption of dietary salts have revealed their specific roles in health and diseases. The effect of dietary salts on metabolic disorders have sparked debate in the field of energy metabolism. A body of literature offers examples on the involvement of dietary salts in human biology and stipulates pathogenic insights into various physiological disorders. Several strategies have been proposed and implemented to deal with the problems that arise from unbalanced consumption of dietary salts. This systematic review examines the role of dietary salts in energy balance and considers the possibility that insights into salts derived signals will stimulate research into novel routes of obesity, diabetes or other disorders of energy balance.

2. Methods

2.1. Search approach and selection criteria

A systematic search was conducted for relevant articles published in English language that identified and defined the associations of dietary salts with metabolic syndrome, obesity, insulin resistance, diabetes and hypertension from medical and biological databases (PubMed, EMBASE and Google Scholar) without placing a limitation on the year of publication date, but using the search subject terms (dietary salts, sodium, potassium, magnesium and calcium intake) and (metabolic syndrome or “MetS”, obesity, insulin resistance, and hypertension). In addition, we used the same search criteria to apply at the Cochrane Controlled Trial Database. We also scanned reference lists of relevant original studies and reviews to identify published peer-reviewed articles. We examined each article according to the following inclusion and exclusion criteria: the study (1) describe the association of dietary salts, sodium, potassium, calcium or magnesium with obesity, diabetes, insulin resistance or hypertension; (2) be an original study published in English; and (3) have key information from laboratory experiments, epidemiological evidence, clinical trials, experimental models, meta-analysis and review articles. We included a wide range of study designs and there was no restriction on the method of dietary salts intake assessment. Laboratory studies, cross-sectional, prospective studies and randomized controlled trials were included. The following studies were excluded: (1) irrelevant to our main objective; (2) cytological studies, and (3) low-quality articles. At first, abstracts were reviewed by 2 authors (Sarwar Hashmi and Safoura Akbari Alavijeh) for inclusion/exclusion criteria. Then, full-text articles were reviewed by according to the same inclusion/exclusion criteria. Articles that seemed to meet all of the criteria were selected for data extraction. All articles were then reviewed and extracted by other authors of the present review article. We are presenting results as a systematic review. The studies of the effects of dietary salts on insulin signaling, obesity, and hypertension included in this review were searched between January 2000 and February 28, 2017. Data from some earlier publications identified through references are also included.

2.2. Data extraction

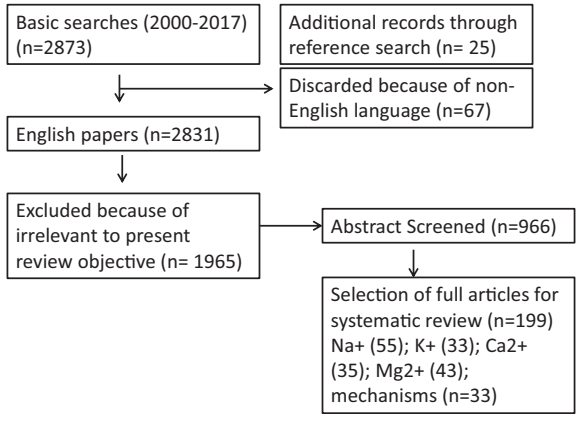
All data were independently extracted by four authors (Sarwar Hashmi, Safoura Akbari, Jun Ling and Christopher Brey). The data of the identified articles were extracted by first author name, year of publication, title of study, journals in which articles were published, dietary salts, metabolic syndrome, diabetes, obesity, hypertension, insulin resistance. The quality of articles was assessed by SH, SA, JL, CB and others. The selected articles were discussed and then final consensus was made on the articles to be included in the systematic review.

3. Results

3.1. Features of the selected studies

We identified a total of 2873 potentially relevant papers in preliminary search. An additional 25 studies were identified through reference lists. After screening of titles and abstracts, we selected 199 full-text articles that met inclusion and exclusion criteria for full-review (Table 1). We divided the present analysis into four categories according to the type of dietary salts: sodium, potassium, magnesium and calcium. The effects of the included dietary salts on insulin signaling, obesity, and hypertension are summarized (Fig. 1) (Tables 2–4). On the basis of their finding

Table 1
Flow chart-search criteria and selection of articles.



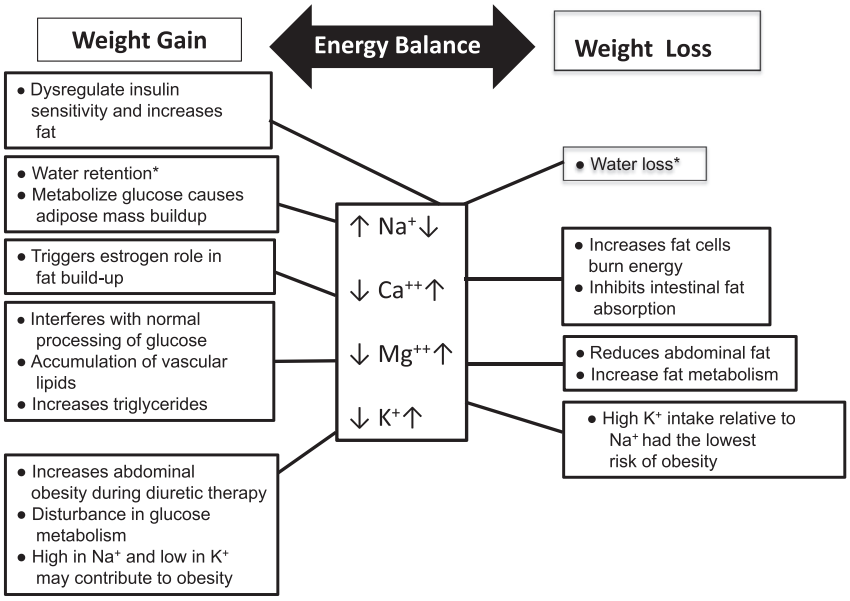


Fig. 1. Effect of dietary salts on mammalian physiology. Dietary salt risk factor levels associated with metabolic disorder in mammals. *Weight attributed to water retention or loss. Up-down arrows indicate an increase or a decrease salt levels.

Table 2
Summary of dietary salts and their implications in promoting resistance or sensitivity to insulin.

Dietary Salt	Intake	Confers resistance or increases sensitivity?	Reference
Na^+	↑	Resistance	8
	↔	Resistance	5, 6, 7
	↑	Sensitivity	6
	↓	Resistance	7, 64
K^+	↓	Resistance	78, 80, 90, 103
	↑	Resistance	88
Mg^{2+}	↑	Sensitivity	130
	↓	Resistance	2
Ca^{2+}	↑	Resistance	165
	↓	Sensitivity	157

The upward ↑ represent an increase in the corresponding dietary salt. The ↓ arrows represent a corresponding decrease in dietary salt and ↔ represents a dietary salt restriction.

related to dietary salts and metabolic disorder, 55 articles examined the relationship between sodium and insulin signaling, obesity, and hypertension; 33 articles evaluated the relationship between potassium and insulin signaling, obesity, insulin signaling, and hypertension; 35 articles assessed the link between calcium and insulin signaling, obesity, and hypertension; and 43 articles evaluated the association between magnesium, insulin signaling, obesity, and hypertension. Thirty three articles looked into the mechanistic of obesity, diabetes, and hypertension (Fig. 2).

3.2. Sodium's effect on metabolic disorder

3.2.1. Sodium in insulin signaling

Sodium regulates the amount of water and pH level in our body, it can negatively impact blood vessels and its high intake can elevate cardiovascular morbidity and mortality because of its effect on blood pressure. However, the effect of sodium is not exclusive to blood pressure but it can also modulate responses to energy stores. A causal inspection of this relationship in diabetic patients led Morales and colleagues to conclude that diabetes develops more often in patients with hypertension [4]. Metabolic differences that exist between high or low Na^+ intake have been further elucidated using data from genetic manipulation in animals. For instance, several in vivo rat data show that a restricted Na^+ intake can lead to insulin resistance and obesity [5–7]. Okamoto and colleagues [6] conducted some tests in Wistar rats and noted that a prolonged Na^+ restriction in those rats increased their body weight and fat buildup, these researchers linked this phenomenon to the observed reduction in glucose uptake suggesting that a strict Na^+ restriction may dysregulate insulin sensitivity and increase fat. To explain Na^+ connection to insulin signaling, Okamoto and colleagues [6] further investigated insulin stimulated glucose transporter-4 gene expression (GLUT4) translocation to the plasma membrane in white adipose tissue of high Na^+ rats then compared this to low Na^+ and zero Na^+ rats. The authors found increased insulin sensitivity in high Na^+ rats which led them to propose that increased insulin sensitivity was related to enhanced GLUT4 gene expression, translocation and insulin signaling [6]. However, more work is needed to clarify the mechanism by which Na^+ influences insulin action to coordinate energy intake and expenditure. According to Ogihara model [8] the high Na^+ intake affects insulin signaling system, is at the downstream of PI3-kinase or *akt* activation, creating insulin resistance, which may contribute to the development of diabetes in patients with hypertension. Phosphatidylinositol (PI) 3-kinase activities associated with IRS and phosphotyrosine in the insulin-stimulated condition increased 2.1- to 4.1-fold, as compared with controls. Insulin-induced phosphorylation of Ser-473 of Akt and Ser-21 of glycogen synthase kinase-3

Table 3
Summary of dietary salts and their implications in promoting obesity.

Dietary Salt	Intake	Obesity Risk	Clinical or Laboratory	Reference
Na^+	↓	High	Clinical	34
	↓	High	Animal model	5, 6, 7, 35, 36, 37
	↑	High	Animal model	23
	↑	High	Clinical	38, 39, 40, 41
K^+	↑	Low	Clinical	98
	↓	High	Clinical	78
Mg^{++}	↓	High	Animal model	138
	↑	Low	Animal model	133, 134
Ca^{++}	↑	Low	Animal model	182, 183

The upward ↑ represent an increase in the corresponding dietary salt. The ↓ arrows represent a corresponding decrease in dietary salt.

Table 4
Summary of dietary salts and their implication in promoting hypertension.

Dietary Salt	Intake	Risk of cardiovascular disease	Reference
Na^+	↑	Increase	8, 54, 57, 65
	↓	Decrease	56, 61, 66, 67, 68, 69
K^+	↑	Decrease	71, 107, 111
	↓	Increase	105, 110, 192
Mg^{++}	↑	Decrease	142, 143, 192
	↓	Increase	144, 145, 146, 147
Ca^{++}	↑	Decrease	169
	↓	Increase	194

The upward ↑ represent an increase in the corresponding dietary salt. The ↓ arrows represent a corresponding decrease in dietary salt.

also increased 2.9- and 2-fold, respectively, in the liver of the high salt–fed rats. Therefore, in both the liver and muscle of high salt-fed rats, intracellular insulin signaling leading to PI3-kinase activation is enhanced and insulin action is attenuated. The hyperinsulinemic-euglycemic clamp study showed that decreased insulin sensitivity induced with a high sodium diet was not reversed by administration of pioglitazone. The following can be concluded: 1) a high sodium diet may be a factor promoting insulin resistance, 2) the insulin-signaling step impaired by high sodium intake is likely to be downstream from PI3-kinase or Akt activation, and 3) this unique insulin resistance mechanism may contribute to the development of diabetes in patients with hypertension.

Hyperinsulinemic-euglycemic clamp studies and glucose uptake into the isolated soleus muscle of Na^+ sensitive (Dahl-S) and Na^+ resistant (Dahl-R) Dahl rat have shown that Na^+ loading for 4 weeks caused hypertension and insulin resistance in Dahl-S rats, but without showing any effects in Dahl-R rats [9]. Moreover, a rise in insulin-induced tyrosine phosphorylation of the insulin receptor and insulin receptor substrates, activation of P13-kinase, and phosphorylation of Akt were also noted in Dahl-S rats fed on a High-Na^+ diet. Addition of K^+ improved the effects of insulin sensitivity in Dahl-S rats fed on High-Na^+ diet and also showed a decrease in blood pressure suggesting an interdependent relationship between insulin sensitivity and Na^+ sensitivity of blood pressure in Dahl-S rats. Hence a diet with K^+ supplement may protect against both hypertension and insulin resistance in Na^+ sensitive individuals [9].

Two major sites of GLUT4 expression are adipose tissue and skeletal muscles where it plays a key role in glucose uptake [10,11]. Several lines of evidence confirm that any alteration in GLUT4 expression in adipose tissue and muscles may lead to enhanced and reduced insulin sensitivity [12,13]. Insulin enables glucose to enter into muscle, adipose and several other tissues. Insulin resistance is specific to the liver and muscle [14] but excess lipid buildup in adipocytes, and unusual lipid buildup in liver and muscle may lead to insulin resistance.

Insulin is synthesized in beta cells of the pancreas and a key regulatory molecule during fat storage. Acting as adiposity signal to the brain for energy balance insulin can have a major impact on both carbohydrate and lipid metabolism. Dysregulation in insulin signaling system can produce widespread and overwhelming effects during fat storage. One mechanism that contributes to insulin signaling system is through PI3-K/Akt activation pathways that consist of several phosphorelay arrangements that play an essential role in the metabolic effects of insulin. Accordingly, insulin activates insulin receptor tyrosine kinase that transfers phosphate group from ATP to tyrosine residues that leads to tyrosine phosphorylation of insulin receptor substrates IRS-1 and IRS-2, the very essential substrates among the IRS family. Following phosphorylation, IRS-1 and IRS-2 bind and activate enzyme phosphatidylinositol 3-kinase (PI3-K) [15,16], which increases serine phosphorylation of Akt (protein kinase B), stimulating glucose transport in the muscle and adipose tissue. Insulin induces phosphorylation/inactivation of Foxo transcription factor which may also be involved in the regulation of glucose and lipid metabolism in liver [17,18]. The ability of sodium to influence insulin resistance has been shown in a rat model [7]. The experiment conducted by Prada et al. [7]. studied the effects of low Na^+ intake on insulin signaling, in JNK activation and in IRS-1ser307 phosphorylation in liver, skeletal muscle and white adipose tissue of Wistar rats. They noted that insulin resistance in response to low Na^+ was tissue-specific which accompanied by activation of JNK and IRS-1ser307 phosphorylation. Thus the rise in RS-2/PI3-K/Akt activity as well as suppression of FOX1 activity in adipose tissue causes lipogenesis which results in visceral fat buildup [7]. Perhaps an enhanced phosphotyrosine phosphatases activity, dephosphorylate IRS-1 [19], then changes in IRS-1 reduces its tyrosine phosphorylation [20]. Although these proposed mechanisms suggest an important role of Na^+ in insulin signaling more studies are needed to broaden our knowledge of the clear mechanistic basis of this association.

In a meta-analysis, the systematic analysis of 37 literature on both randomized and non-randomized trials on Na^+ restriction and glucose tolerance was conducted [21]. The analysis of 20 randomized crossover trials on 504 individuals and 9 non-randomized crossover trials on 337 individuals did not show any change in circulating glucose levels in fasting individuals on reduced Na^+diets. But the 19 of the 20 randomized, crossover trials on 494 individuals on reduced Na^+ diet showed high levels of insulin. Nine nonrandomized trials on 337 individuals with reduced Na^+ diets did not indicate alteration in fasting insulin level. According to authors, these data were not consistent across sensitivity analyses. Based on their meta-analysis the authors suggested extended intervention durations, ensuring comparability of groups through randomization, and evaluating sodium intakes relevant to sodium reduction in population and a need for comparable measures of glucose tolerance across studies [21].

A recent Cochrane database systematic analyses argue that limited Na^+ intake reduces body water contents, but this loss is balanced by elevated epinephrine, renin, and angiotensin levels, which then inhibits insulin action and thereby increase insulin resistance [22]. High Na^+ diet is a risk factor for cardiovascular diseases but, the effect of low Na^+ diets in insulin resistance is not yet clear. However, there are three mechanism that describe the connection between low Na^+ diet and decreased insulin resistance 1) low Na^+ intake lowers blood leptin levels resulting in a reduction in size of abdominal fat cells, causing reduced obesity and insulin resistance [23,24], 2) low Na^+ diet regulates GLUT4 expression, leading to a reduced insulin resistance [4,25] and 3) low Na^+ diets bring about changes in angiotensin II level affecting insulin action [26]. Although there have been intensive investigations on the relationship between Na^+ intake and insulin resistance there are

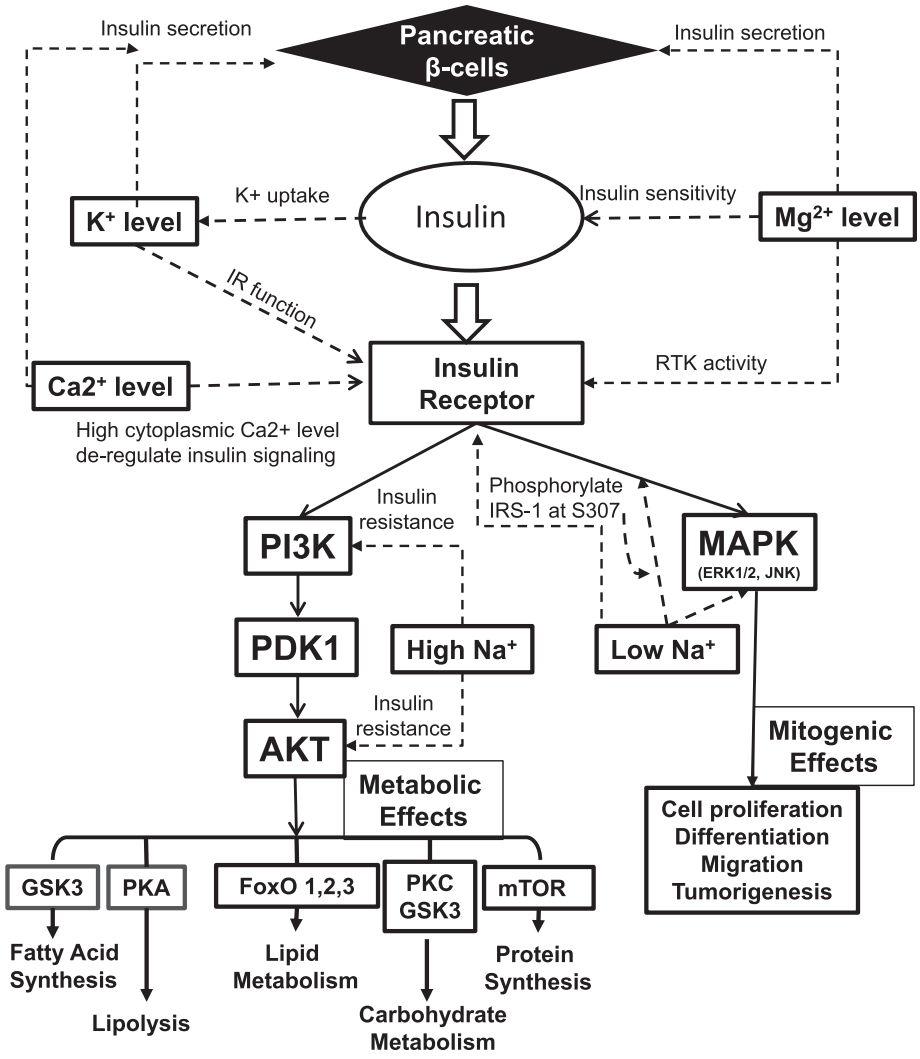


Fig. 2. Mechanisms of regulation of metabolisms and cellular processes by magnesium, potassium and sodium via insulin signaling pathway. Key biochemical regulatory points are illustrated in the diagram above. Kinases and transcription factors listed downstream AKT to regulate metabolism are key factors but not inclusive of all other pathways. The interactions among these salts (e.g. Mg^{2+} regulate Na^{+} and K^{+} balance through Na^{+}-K^{+}-APTase pump) and their physiological effects on obesity, diabetes, and hypertension are described in the text. IR: insulin receptor; IRS-1: insulin receptor substrate-1; RTK: receptor tyrosine kinase.

inconsistencies in the final results [27]. These inconsistencies may be because of flexible definitions for 'low Na^{+} intake and differences in the length of research. Oh et al.) [27] argued for conducting more randomized controlled studies including proper experimental validation concerning the effects of Na^{+} diet on obesity and insulin resistance.

In one study, the alteration in sodium sensitivity and insulin sensitivity was also examined after a continued sodium burden in 17 elderly populations [28]. It was found that high Na^{+} diets did not change Na^{+} sensitivity, the high insulin sensitivity found at high Na^{+} diets after one week did not continue after a longer Na^{+} diets [28]. Townsend et al. [29]. noted an association between one week of Na^{+} overload in healthy individuals with higher insulin sensitivity when compared to Na^{+} restriction. These inconsistent findings may be the variation in protocols and disease association. Several studies via euglycemic-hyperinsulinemic clamp methods have demonstrated a profound connection between high Na^{+} diets and insulin resistance in human [30,31] and animal [8,9].

A study of 28 healthy individuals (13 men and 15 women) with a family history of hypertension did not show any relationship between insulin sensitivity and Na^{+} sensitivity after 1 week of sodium restriction and after 1 week of sodium loading [32]. There was an inverse relationship of sodium sensitivity to plasma renin activity and plasma aldosterone in men; sodium sensitivity in women was directly linked to sodium-stimulated body weight gain [32]. In Melander's. study high Na^{+} diets altered glucose clearance in men which was greatly associated with sodium sensitivity, plasma renin activity, and plasma aldosterone levels, but there was no similar association in women, suggesting a complicated interaction among sodium intake, the renin-angiotensin-aldosterone system, and insulin sensitivity as well as possible difference in endocrinological regulation between men and women [32].

3.2.2. Sodium in lipid metabolism involved obesity

Our knowledge about the regulatory role of Na^{+} in obesity has progressed rapidly [33] and now there is growing agreement among scientists that a strict restriction on Na^{+} diets influence fat deposits. This led to explore novel ways to identify and manage obesity. To obtain an independent proof most experimental tests on the effects of dietary Na+ on fat deposits depend on feeding sodium diets to test animals and then measuring the fat contents or adipose mass. The reports published by several laboratories [7,34,35] have

included both clinical and rat models, where a strict restriction on Na^+ were shown to increase plasma triglycerides and total cholesterol levels. A low Na^+ diet increases fat buildup in the body, probably because of its stimulating effects on the activity of fat synthesizing enzyme [36]. The insulin resistance that developed from low Na^+ diets can reduce lipoprotein lipase activity and may influence the release rate of non-esterified fatty acid (NEFA) from adipose tissue. A Na^+ restricted diet may also increase aortic wall lipid storage in moderately hyperlipidemic mice [37].

Several animal studies suggest that rats with high Na^+ intake leads to an elevated plasma leptin and an excessive buildup of white adipose fat compared with rats fed on low Na^+ diet. Using a rat model, Fonseca et al. [23]. sought to experimentally determine whether Na^+ influences glucose metabolism. They found an enhanced glucose metabolism and an insulin response in rats fed on high Na^+ diets, suggesting that high sodium-diet enhances adipocytes ability to metabolize glucose and that may cause adipose mass buildup. On these lines of research several other labs investigated the relationship between sodium intake and fat buildup. For example, a group study while examining various age groups including adolescent [38] and adult [39] subjects found a positive association of Na^+ consumption with excessive body fat buildup that was independent of food intake. Later, a cross-sectional study on adolescent subjects showed a positive relationship between Na^+ intake and subcutaneous abdominal adipose tissue [40]. High Na^+ concentration can conceivably add to excessive fat buildup that may be independent of energy intake. A recent analysis of data from the rolling cross-sectional study-the UK National Diet and Nutrition Survey including 458 children and 785 adults, found a positive link between high sodium diets and fat mass increase in both children and adults suggesting that high sodium diet may increase the chances of obesity that is independent of energy intake [41]. One possible explanation is that salty diets in addition to thirst can also increase hunger or a desire to eat which prompt people to eat [42]. Although most proposed mechanisms lead to the idea that Na^+ can directly increase body fat [38–40] at the moment the conventional point of view is that metabolic responses elicited by Na^+ salt differ based on the Na^+ intake.

It is fairly clear from studies in both children [43] and adults [44,45] that dietary Na^+ intake may be positively connected to adiposity. Several cross-sectional studies involving children from three continents have shown a positive relationship between Na^+ diets and the intake of sugar-sweetened drinks [46–48]. Although there is relationship between Na^+ intake and adiposity, this association is independent of energy intake [43]. The reports from animal studies show that a high Na^+ diet increases adipose tissue mass and it is because of changes in insulin and glucose metabolism that supports fat build-up [23,25]. For instance, male Wister rats fed on a high Na^+ diet showed substantial growth in adipose tissue mass at week 6 than rats fed on a normal sodium diet, by week 9, adipose tissue mass remained the same between the groups [23]. The expanding understanding of the impact of sodium diets on blood pressure has produced a number of fruitful avenues to investigate the impact of a high sodium diets on other health issues.

3.2.3. Sodium in hypertension

The fundamental interest in Na^+ for its role in blood pressure has developed over the years is a realization that salt is not only involved in high blood pressure but it can also cause other important human diseases. There is clear correlation between hypertension and insulin resistance, and patients with diabetes are known to have increased blood pressure responsiveness to salt loading. Reasonable explanation of links between associations of insulin resistance and hypertension are 1) hypertension per se may increase the risk of insulin resistance due to decreased capillary density and 2) insulin resistance may increase the risk of hypertension by several ways. Obesity is one of the primary causes to insulin resistance. The energy and sodium intakes of obese subjects are higher than that of subjects with normal weight. The plasma insulin levels of insulin resistant subjects are increased, and insulin increases sodium reabsorption from the kidney tubuli. Thus, obese insulin resistant subjects eat more sodium salt and are at the same time more Na^+ sensitive than normal-weight subjects with normal insulin sensitivity.

The magnitudes of epidemiological, clinical and experimental studies have found insulin resistance and hypertension traced to the amount of Na^+ in human diets. It is approximately about 30 years when a direct evidence was provided on the linkage between hypertension and insulin resistance [49]. Then series of clinical studies proposed that patients with insulin resistance acquire a tendency to develop sodium sensitive hypertension [50–52]. It is widely speculated that genetic and other factors such as excess fat buildup (obesity) are likely culprits causing hypertension [53]. In recent years, there have been renewed interest in Na^+ in attempt to manage a number of pathological conditions, including stroke, heart disease, and even kidney disease. High Na^+ intake can increase blood pressure [54] which may become a risk factor for cardiovascular diseases; however, it is not clear if high Na^+ intake directly leads to cardiovascular disease? Earlier studies have shown that alterations in Na^+ intake lead to changes in plasma Na^+ concentrations [55–57] that may affect blood pressure. A rise or drop in Na^+ intake results in changes in plasma sodium concentration, affecting extracellular volume, and that can bring changes in blood pressure. For instance, in patient with high blood pressure and variations in plasma Na^+ is directly linked to the response of renin-angiotensin system, which affects plasma renin activity [58].

While more data is needed to explain the precise mechanism whereby insulin resistance is linked to hypertension, several factors such as the dysregulation of central nerves including leptin hormone, and the activation of renin-angiotensin system (RAS) are believed to play a role linking insulin resistance and hypertension [59]. The effects of insulin on WNKs activity have been associated with sodium sensitive hypertension. There is strong evidence that protein kinase B (PKB) mediates the phosphorylation of WNK1 but WNK1 phosphorylation does not regulate its kinase activity. Together, these results clearly highlight an association between the PI3-kinase/PKB pathway and WNK1, which may affect blood pressure [60]. Dietary Na^+ intake is positively correlated with blood pressure, and in patients with type 2 diabetes (T2D), salt restriction confers a modest reduction in blood pressure [61] and that Na^+ supplementation reduced the antihypertensive efficacy of blood pressure lowering agents [62]. The fundamental details underlying the effect of Na^+ on blood pressure and the relationship between Na^+ intake and mortality in patients with T2D is not well understood. Perhaps, blood pressure lowering effect associated with reduced Na^+ intake may be translated into protection from end-organ damage. Reduced Na^+ intake is associated with activation of metabolic and neurohormonal pathways, including the sympathetic nervous system [63] and reduced peripheral insulin sensitivity [64]. Recently, Horikawa and collegues have shown a clear association of high dietary Na^+ intake with increased incidence of cardiovascular diseases in patients with T2D [65]. There is a general belief that low sodium diets may help prevent the occurrence of high blood pressure and hypertension [66–69]. Contrary to Na^+, the K^+ is known to relax blood vessels as well as expel Na^+ that results in lowering blood pressure. In addition to higher Na^+ intake, a low level of K^+ intake and some other factors have major effects on blood pressure. One clue that might be drawn from the data summarized here is that maintaining a balance in Na^+ intake is critical for normal human health.

Low sodium diet lowers blood pressure both in individuals with normal blood pressure and in patients with hypertension. A 12-week dietary approach to stop hypertension (DASH) diet trial indicated that reducing sodium salt from the normal 8 g per day to 4 g per day lowered blood pressure among hypertensive, normotensive individuals [67] and non-acutely ill adults. A 2013 Cochrane review [70] and an inclusive meta-analysis of data on the control of dietary sodium, have also identified its effectivity in non-acutely ill adults, and then underlined the effectiveness of very low sodium diets. The authors of Cockrane review [70] noted that a simple reduction in sodium intake for four or more weeks resulted in reduce blood pressure in both hypertensive and normotensive individuals, irrespective of sex and ethnic group. They also found that reduction in sodium diets also linked to a small physiological increase in plasma renin activity, aldosterone, and noradrenaline and no significant change in lipid concentrations [70]. Thus a reduced sodium diets can lower blood pressure and thereby reduce cardiovascular disease. Also, a systematic review completed by WHO Nutrition Policy and Scientific Advice Unit maintained that reduced sodium intake although lowers the blood pressure shows no negative effect on blood lipids, catecholamine levels, or renal function in non-acutely ill adults. Lower sodium intake has also been linked to low risk of stroke in adults [71]. An extensive literature search suggests that if the amount of sodium reduction starts at daily intake of 5 g or less then it shows positive health effects and in addition to this, the presence of somewhat high potassium in a low sodium diets may give rise to extra benefit on blood pressure [71,72].

In their comprehensive review that was published in 2009, He and colleagues [73] suggest that a reduction in the amount of Na^+ should begin early in life. According to Tekol [74] some of the cardiovascular effects of continued high sodium intake may be irreversible. On the basis of 15 randomized controlled studies on 167, 656 participants, the World Health Organization (WHO) published its report in 2012 suggesting that low sodium diets not only lowered average blood pressure but also the incidence of stroke and heart diseases [22,75]. This suggest that although low sodium intake lowers blood pressure it increases blood renin, aldosterone, noradrenaline, adrenaline, cholesterol, and triglyceride levels.

The effects of sodium on the vascular system are much more complicated. According to experimental animal studies, high sodium intake does not only increase baseline blood pressure but also blood pressure responsiveness to vasoconstrictors like angiotensin, reflecting increased reactiveness of small resistance vessels. High sodium intake results in structural and functional changes in arterial channel (stiffening of large arteries) and to left ventricular hypertrophy. High sodium diets suppress the function of renin-angiotensin system. Although we do not know much about the exact mechanism yet, the endothelial dysfunction may play a critical role on the effect of excess Na^+ intake on blood pressure. Various rat models have proven to be valuable to gain insight on the connection between sodium and hypertension [76].

3.3. Potassium's effect on metabolic disorder

3.3.1. Potassium in insulin signaling

Potassium is a vital salt involved in many cellular function [77] including metabolism. Potassium also maintains total body fluid volume and electrolyte balance. Serum K^+ is regulated through homeostatic system that is influenced by K^+ intake, excretion and the factors that affect its partitioning between intracellular and extracellular spaces. Low serum K+ level is connected to incidence of metabolic syndrome in middle-aged and elderly Chinese. Sun and colleagues [78] found in their cross-sectional study with 10341 subjects aged 40 years or older the prevalence of metabolic syndrome was 52% in subjects with hypokalemia compared with a prevalence of 38% in subjects with normokalemia. However, Hyperaldosteronism, and hypercorticolism, the use of liquorice products and the use of large doses of non-potassium sparing diuretics are the most common causes of hypokalemia. The effect of K^+ deficiency in glucose intolerance during energy deficiency was also investigated [79] It was found that K^+ deficiency gave rise to insulin resistance whereas increasing K^+ levels reversed problem [79]. In support of this study, there is well substantiated evidence that K^+ is involved in the regulation of insulin receptor function as well as insulin secretion by pancreatic β−cells [80]. To assess the role of K^+ in insulin secretion and function, a clinical trial was conducted that involved human subjects having a normal glucose tolerance level [81]. In this study, K^+ deficiency was measured by drop in plasma K^+ as well as decline in total body K^+; declines in K^+ was associated with the drop in insulin release. The outcome of this study led investigators [81] to propose that reduced K^+ prompted to decrease pancreatic β-cell sensitivity and hyperglycemia are interconnected events. In a subsequent clinical trial, experimentally generated hypokalemic subjects demonstrated impaired glucose tolerance but addition of K^+ rescued the defect in insulin release [82]. While there is a considerable level of inverse correlation between serum K^+ level and blood glucose, the addition of K^+ has been shown to reduce this effect [83]. The effect of K^+ deficiency on metabolic disorders is mediated partly by weakening of endothelial function. One mechanism that may contribute to this effect is through nitric oxide which is necessary for endothelial function [84], a reduced K^+ levels can also reduce nitric oxide levels which can lead to endothelial dysfunction, causing insulin resistance, and glucose intolerance. Recent population-based studies have demonstrated that lower dietary K^+ is associated with new onset diabetes in African-American population [85]. Low dietary potassium is more common in African Americans than in whites. More recent data from the Atherosclerosis Risk in Communities (ARIC) study including diabetes free 2716 African American and 9493 white population concluded that low serum K^+ levels in African Americans may contribute to their excess risk of T2D relative to whites [86].

Low plasma K^+ level has been found in obese patients who were subjected to thiazide treatment [87], whereas increasing K^+ intake has positive effect on human health. Mariosa and colleague observed in their cross-sectional study that the mean plasma potassium level of obese subjects receiving thiazides was 4.3 mmol/l compared to 4.4 mmol/l of subjects not receiving diuretics [87]. While the difference in plasma potassium levels differed statistically, the plasma potassium level of 4.3 mmol/l is by no means low, and not even close to levels of hypokalemia (less than 3.4 mmol/l). Lee et al. analyzed data from the Korean National Health and Nutritional Examination Survey (2008–2010) and found that K^+ intake to be inversely associated with an increased risk of metabolic syndrome, which was found to be more significant in postmenopausal women, but not among men. Higher K^+ intake reduces the incidence of metabolic disorder in women [88].

The cellular uptake of K^+ is essentially dependent on insulin, but hyperglycemia can stimulate K^+ uptake with increased participation of passive transfer processes [89] Short-term K^+ deprivation can result in insulin resistance for cellular K^+ uptake, leading to changes in muscle Na^+/K^+-ATPase expression [90]. Sodium and potassium salts are components of the cell membrane enzyme Na-K ATPase that is involved in the water and nutrient transport across the cell membrane. The Na^+/K^+-ATPase level is decreased in skeletal muscles, heart, and nerves [91,92] in diabetic patients, and there is report that in some instances the K^+ supplementation did increase muscle Na^+/K^+-ATPase [93]. It is therefore possible that dietary K^+ may play a preventive role against diabetes [94]. In addition to insulin response, there is probably more delicate but

important association between the muscle Na/K ratio and energy used in individuals prone to T2D [92]. The clinical as well as animal studies indicate independent regulation of glucose and K^+ transport which occurs within the framework of an intricate insulin-stimulated system prompted by the binding of insulin to the insulin receptor tyrosine kinase. The insulin's actions on glucose and K^+ uptake are independently regulated by dietary fat and K^+ content, respectively [95]. In order to determine if insulin influences cellular K^+ uptake, Choi et al. [95]. conducted a comprehensive study on rats fed on high fat diet. Although their data did not show a substantial decrease in plasma K^+ level, it did indicate a sizable reduction in insulin-stimulated cellular K^+ uptake in the high-fat diet rats. In addition, the urinary K^+ excretion was also found to be low in those rats fed on a high-fat diet, pointing to a reduced K^+ intake. There was no change in insulin-stimulated cellular K^+ in rats with the same K^+ intake on either a high-fat or a control diet. It is important to note that insulin regulates both Na^+ and K^+ thus there is a possibility of interactions between the two systems. Insulin's effects on glucose and K^+ cellular uptake are independently regulated. An assessment of the connection between K^+ restriction and cellular mechanism activity in maintaining plasma K^+ levels, indicated that reduced dietary intake for two weeks had no effect on plasma K^+ level, aldosterone concentration, muscle Na^+/K^+-ATPase or renal Na^+/K^+-ATPase expressions. However, a remarkable reduction was apparent in both insulin-stimulated cellular K^+ uptake and renal K^+ maintenance [96].

3.3.2. Potassium in lipid metabolism related with obesity

We know remarkably little about the role of K^+ in lipid metabolism. Although few studies have shown a perfect correlation between low K^+ presence and disorder of glucose-lipid metabolism the mechanisms that control K^+ effects on obesity are not well-understood. Recently, Cai et al. [97]. conducted systematic review and meta-analysis based on epidemiological evidence where they pooled data to evaluate the inclusive effect of K^+ on obesity and noticed that high K^+ did not lower the risk of obesity, however, serum K^+ and urinary Na^+ to-K^+ ratio were linked to obesity; nonlinear analysis showed a shielding effect of K^+ on obesity and metabolic syndrome. Further studies are required to test the primary mechanism. The patients with the highest K^+ intake relative to Na^+ have been shown to have the lowest risk of obesity [98]. Notably insulin resistance can cause fat buildup because of over-activation of Renin Angiotensin-System (RAS) [99]. The targeted disruption of RAS has been found to increase insulin sensitivity and provide protection from high-fat diet-induced obesity and the data from both human and animal studies shows over-activated systemic RAS in obesity [99]. Normally essential hypertension is a sodium retention state. The circulating blood volume is not increased, but the venous volume is concentrated to central parts of the circulation. Increased baroreceptor load leads to decreased cortical sympathetic outflow and decreased plasma renin levels. Normally during sodium restriction, and probably also when using appropriate low-dose HCT-treatment, renin levels increase to the levels seen among normotensive subjects. The effects of an inappropriately large HCT-dose can of course be different. The RAS model provides a common underlying mechanism to explain the connection between abdominal fat buildup, K^+ reduction and the changes that take place in glucose homeostasis during diuretic therapy. Thiazide diuretic activates RAS in response to volume contraction, which can reduce serum K^+ [100], and suppression of RAS activity protects against T2D progress.

To experimentally investigate the effect of diuretic treatment in hypertensive patients on thiazide therapy, Mariosa and colleagues [87] studied 329 hypertensive patients without known diabetes or impaired renal function and found that obese patients on diuretic therapy had lower plasma K^+ and higher glucose compared with patients on diuretic therapy but without obesity. Based on these data, the authors proposed that fat buildup prompts K^+ loss during diuretic therapy that may affect glucose homeostasis. However, cause-relationships cannot be drawn from cross-sectional settings, were the blood pressure medications were not selected on a random base. Renin Angiotensin-System serves as a link between obesity and insulin resistance, its activation promotes hypertension in obese individuals. The identification of a functional RAS in mammalian adipose tissue, and expression of many of the RAS components in adipocytes has now been established [101]. It appears that obesity and its connection with hypertension are coupled with changes in RAS gene activity in adipocytes. Further, increased RAS components have been observed in obese individuals which decreased substantially after weight loss [102]. Studies involving animal model with targeted disruption of RAS genes have shown increased insulin sensitivity as well as protection from fat buildup. Low K^+ results in the weakening of vascular relaxation which causes hyperglycemia and insulin resistance [103]. Although little is known about the exact mechanism the majority of published work to date clearly indicates the importance of K^+ in obesity.

3.3.3. Potassium in hypertension

Potassium functions with Na^+, Ca^{2+} and Mg^{2+}, is crucial to heart and plays a key role in skeletal and smooth muscle contraction, making it an important salt for normal digestive and muscular function. Potassium requires Mg^{2+} to maintain its own normal cellular concentration [104]. Insufficient Ca^{2+} and K^+ intake can cause high blood pressures and high Na^+ diets can also elevate blood pressure. Thus it is logical to surmise that K^+ can help lower the blood pressure by a simple mechanism of balancing the effect of Na^+ and other salt. This relationship has been shown in multiple studies. For example, K^+ deficiency increases blood pressure [105], Na^+ sensitivity [106], and increase the risk of cardiovascular morbidity [107] and mortality [108]. The effect of K^+ on blood pressure has been addressed in multiple studies but the outcome of those studies were inconsistent which created confusion. To clarify the perplexity, Whelton and colleagues [105] conducted a meta-analysis including 2609 human subjects included in 33 randomized controlled clinical trials in which K^+ supplementation made the difference between the intervention and control conditions. The authors suggested that low K^+ intake may be important factor in the genesis of high blood pressure. This led them to propose that increased K^+ intake may be recommended for prevention and treatment of hypertension. Blood pressure lowering effects of K^+ supplementation depend on the baseline K^+ and Na^+ intakes and can be seen, when the habitual K^+ intake is low and that of the Na^+ intake high. Potassium supplementation decreased blood pressure only in subjects with 24-hour urinary Na^+ excretion over 165 mmol (more than 9.5 g salt/day) [105]. Potassium is a mild diuretic and it increases sodium excretion which clarifies the findings of the meta-analyses. A recent Cochrane database systematic analyses [109], did not find statistically significant blood pressure lowering effects of K^+ supplementation, however, the authors noted that because of insufficient number of participants in two trials, the short duration of follow-up, and the unexplained heterogeneity between trials, their result is inconclusive. Several other epidemiologic data show that hypertension is more prevalent in populations taking low-K^+ diets [110]. A series of epidemiological and clinical data as well as experimental results in animals have shown that increasing K^+ intake lowers blood pressure, reducing the risk of stroke and preventing the development of renal disease [111].

Potassium deficiency and/or low dietary K^+ intake play a key role in the regulation of blood pressure in patients suffering from hypertension and diets containing more K^+ and less Na^+ can reduce the risk of high blood pressure and stroke. In animal models, K^+ has

been shown to inhibit vascular smooth muscle cells proliferation, platelet aggregation, and arterial thrombosis [112–114]. Several experimental trials show that increasing K^+ intake reduces cardiovascular disease mortality. This is mainly attributable to the blood pressure-lowering effect and may also be the direct effects of K^+ on the cardiovascular system. Reduced serum K^+ increases the risk of lethal ventricular arrhythmias in patients with ischemic heart disease, and heart failure whereas increasing K^+ intake may help reduce this risk. In a recent review article, authors have provided an almost complete summary of 11 cohort studies and 22 controlled trials on the influence of K^+ on blood pressure [115]. Results from cohort studies in adults and also the data from four controlled trials and cohort studies in children indicates increased K^+ consumption reduces blood pressure in adults, with no adverse effects on blood lipids, hormone levels or kidney functions. Thus as discussed in detail it is now possible to model the influence of K^+ on blood pressure and validate the model by clinical trials on a range of patients suffering from blood pressure. A chemical communication of K^+ with Na^+, Ca^{2+} and Mg^{2+}, is crucial for heart function, because the interaction among these salts are important in both skeletal and smooth muscles contraction.

3.4. Magnesium effect on metabolic disorder

3.4.1. Magnesium in insulin signaling

Magnesium performs numerous critical functions in human's health and diseases. Magnesium controls the activities of essential enzymes that are involved in digestion, absorption, and the utilization of fats; it is a critical cofactor of many enzymes in carbohydrate metabolism. Similar to K^+, Mg^{2+} is a principal intracellular cation and an imbalance in Mg^{2+} levels can be accompanied by secondary K^+ depletion [104]. This may be the reason why various metabolic effects of K^+ are modulated and/or amplified by Mg^{2+}. Although Mg^{2+} and K^+ have distinct cellular roles, they may be subject to similar abnormalities such as cell leakage, for example, in the case of metabolic acidosis. Magnesium helps to activate the enzymes in our body and maintains the electrolyte balance, it regulates blood sugar levels and is involved in the functioning of heart and immune system. Recent progress in magnesium research has established a link between Mg^{2+} intake and metabolic disorder. Animal studies indicate a key role of Mg^{2+} in insulin secretion and action and its intake is possibly inversely related to the risk of hypertension and T2D mellitus. In addition, several clinical studies have shown a strong association between serum Mg^{2+} and metabolic syndrome [116,117].

Magnesium is required for both proper glucose utilization, insulin signaling [118,119], energy production, oxidative phosphorylation, glycolysis and synthesis of DNA, and RNA. Magnesium is important to enforce insulin action and there is a strong connection between serum Mg^{2+} and glucose clearance. Yajnicks et al. [120]. have observed a change in glucose clearance with a greater sensitivity to insulin during sufficient amount of Mg^{2+} presence. Low Mg^{2+} levels have frequently been observed in individuals with T2D, it can reduce secretion of insulin in pancreas, whereas a high Mg^{2+} level has been linked to low fasting glucose and insulin [121]. Type 2 diabetes is frequently linked to hypomagnesaemia [122]. Thus genetics, poor diets, changes in insulin metabolism, and persistence metabolic acidosis, can aid to hypomagnesaemia in diabetic patients [123]. Low Mg^{2+} presence stimulates the weakening of the renal function in T2D patients [124]. It has been shown that addition of dietary Mg^{2+} improved glucose management and insulin response in ageing and non-insulin-dependent diabetics [125]. Because of its importance in human health, several laboratories have focused attention on the issue of dietary Mg^{2+} consumption. Decade old findings have shown an inverse association between Mg^{2+} uptake and the risk of diabetes mellitus is also of particular interest [126,127].

Both insulin and low glucose levels allow fat mobilization to help increase hormone sensitive lipase (HSL) production that is needed to break down and mobilize fat in the adipose issues. A possible protective role of dietary Mg^{2+} in insulin resistance has also been proposed [128]. In uncontrolled T2D, the low intracellular Mg^{2+} presence negatively affects tyrosine kinase activity at the insulin receptor level [129,130] and there is a report of 10% increased insulin sensitivity and 37% reduced blood sugar with oral Mg^{2+} supplement [130]. Magnesium has long been known to play a critical function in Na^+ and K^+ transport across cell membranes, it activates Na^+-K^+-ATPase pump while regulating Na^+-K^+ transport and therefore its reduction can alter membrane bound Na^+-K^+-ATPase activity [131], which is an important step to maintain glucose transport. There is a report of a considerable inverse correlations of serum Mg^{2+} with Triglycerides, VLDLc and a positive correlation with HDLc in diabetic patients [132].

In an experiment which lasted for two months, researchers [133] investigated the effects of Mg^{2+} supplement on serum thyroid hormone and lipid levels in alloxan-induced diabetic rats. They found that Mg^{2+} supplement lowered total cholesterol and triglyceride levels in diabetic rats to the control level and concluded that oral Mg^{2+} decreased the diabetes-induced disturbances of lipid metabolism. Similarly, there was substantial decrease in total cholesterol, LDL cholesterol and triglycerides but a rise in HDL cholesterol after continued Mg^{2+} supplement for 12 weeks [134]. The data obtained from these experiments thus imply that Mg^{2+} supplement gives a positive effect on the lipid profile of T2D patient. Magnesium deficiency contributes to vascular lipid deposits and the low removal of circulatory triglycerides is perhaps the key mechanism that contributes to hyperlipedemia. Magnesium plays important role as a second messenger for insulin [135,136]. Insulin boosts intracellular Mg^{2+} uptake [137]. Likewise, hypomagnesaemia may stimulate changes in glucose transport, lower insulin secretion, and modify insulin–insulin receptor interactions [123] thereby exaggerate insulin resistance [2].

3.4.2. Magnesium in lipid metabolism-related with obesity

Magnesium does play a role in energy production. In the plasma of rat fed with high carbohydrate diet the Mg^{2+} deficiency has been found to enhance triglycerides and free cholesterol levels but decrease esterified cholesterol levels [138]. Rayssiguter and colleagues [138] noted that acute Mg^{2+} deficiency in weanling rats produced hypertriglyceridemia, a reduced percentage of cholesterol transport by HDL lipoprotein and a reduction in LCAT activity. The mechanism by which Mg^{2+} perform these functions because it activates lecithin cholesterol acyltransferase (LCAT) and lipoprotein lipase (LPL), which lowers triglyceride levels and raises HDL-cholesterol levels and hence its deficiency can contribute to vascular lipid buildup [104]. Magnesium may increase cholesterol, VLDL, LDL, triglyceride-rich lipoproteins and a reduced HDL [139]. Moreover, Mg^{2+}-ATP is also a controlling factor for the rate-limiting enzyme in the cholesterol biosynthesis. Magnesium supplement to hyperlipidaemic subject reduces LDL cholesterol and triglyceride [140]. Rabbits fed with Mg^{2+} deficient and cholesterol enriched diet accelerated arterial thickening in the intimal layer of aorta by high lipid deposits in the arterial wall, however, providing $Mg^{2+}$to those rabbits lowered serum cholesterol and triglycerides and attenuated the progression of atherosclerosis in Mg^{2+}deficient rabbits [141]. These findings establish an essential role of Mg^{2+} in lipid metabolism.

3.4.3. Magnesium in hypertension

Magnesium regulates vascular smooth muscle contraction and can influence blood pressure and pathophysiology of hypertension [142,143]. The importance of Mg^{2+}in enzymatic activity is well

founded in vascular contraction; low Mg^{2+} can alter vascular smooth muscle cell function in hypertension. In fact, a few clinical trials have found lower than normal Mg^{2+}levels in hypertensive subjects suggesting that Mg^{2+} deficiency can negatively affect blood pressure [144]. Ma and collegues [145] studied 15248 individuals aged 45–64 years and found an inverse relationship between serum Mg^{2+} levels in hypertensive white men and women, and in black men, to systolic blood pressure. There are several key observations on hypertensive individuals with obesity, and insulin resistance which show clear sign of hypomagnesaemia [146] and there are some studies showing an inverse relationship between Mg^{2+} intake and blood pressure [147]. Considerable epidemiological data linking Mg^{2+} and blood pressure came from the Honolulu Heart Study [148], which included 61 dietary variables in 615 Hawaiian men participants of Japanese origin without having history of hypertension. Based on these data, dietary Mg^{2+} consumption showed the strongest inverse association with blood pressure.

Many cardiovascular disorders are associated with changes in Mg^{2+} levels; in particular, those affecting the myocardium function [149]. It is also known as Ca^{2+} antagonist influencing Ca^{2+} channels in vascular smooth muscle cells and because it has considerable arterial blood pressure-lowering effect, it can cause low peripheral and cerebral vascular resistance. Hypertension can be a direct result of an elevated Ca^{2+} influx as well as arterial smooth muscle cells contraction [149–151]. Magnesium is important in the control of blood pressure, primarily via the regulation of vascular membrane Mg^{2+}-Ca^{2+} exchange sites. High dietary K^{+}/Mg^{2+} have additive effects in preventing an increase in Na-K pump inhibitor (SPI), thus likely preventing a blood pressure increase [152]. Potassium has a protective role in cardiovascular diseases and its reduction along with Mg^{2+} can play a key role in the genesis of cardiac arrhythmias [153]. In pathological state, Mg^{2+} and K^{+} deficiency often occur concurrently and it happens that K^{+} deficiency becomes an exaggerating factor in disease pathology. For example, the loss of both cellular Mg^{2+} and K^{+} may lead to the progression of the initial lesion in the arterial wall. Magnesium deficiency induces arterial damage, a loss of Mg^{2+} and K^{+} and an increase in the Ca^{2+} and Na^{+} content of the cell may affect different stages of arteriosclerosis and that K^{+} deficiency may intensify the pathology. Substantial experimental evidence has now accumulated from animal models that suggest magnesium-induced relaxation in smooth muscle [154,155]. Despite the evidence that have been gathered from large bodies of research on the involvement of Mg^{2+} in blood pressure, much remains to be discovered whether or not Mg^{2+} is directly linked to the development of blood pressure.

3.5. Calcium effect on metabolic disorder

3.5.1. Calcium in insulin signaling

Calcium is an essential micronutrient with many biological functions. Either in its free ion or bound complexes Ca^{2+} is required in bones, muscles, heart and digestive system and serves as a second messenger, its deficiency may lead to many biological disorders. Many of the reports about the effects of Ca^{2+} on metabolic disorder have come through a series of cellular and animal studies. In one study, Hagström and colleague [156] noted higher than normal serum Ca^{2+} levels in diabetic individuals. They further noted that the differences in Ca^{2+} levels between diabetic and non-diabetic individuals was because of impaired insulin sensitivity but not because of defective insulin secretion. A low Ca^{2+} intake triggers parathyroid hormone (PTH). High PTH may stimulate Ca^{2+} channel to increase Ca^{2+}influx and thereby elevate intracellular Ca^{2+}levels, which in turn influence insulin sensitivity and hypertension [157]. High intracellular Ca^{2+} lowers the effects of insulin in adipocyte. According to a model high intracellular Ca^{2+} may reduce glucose transporters (GLUT4) as well as reduces insulin receptor activity [158]. Insulin secretion is a Ca^{2+} dependent process. Alterations in insulin secretion can result in blood glucose homeostasis disorder and the change in amount of Ca^{2+} in main insulin target tissues enhance peripheral insulin resistance [159–162] by weakening insulin signal transduction that results in low GLUT-4 activity [162,163]. The presence of high levels of Ca^{2+} can cause a number of metabolic abnormalities, including impaired glucose tolerance [164]. The observation that low insulin sensitivity and insulin secretion [165] can promote diabetes has led to the proposal that these factors may also impair glucose tolerance [166]. As such serum Ca^{2+} concentration and calcium-phosphate product have been found to have a link with the development of T2D, however, these associations are independent of the effect of adiposity, glucose tolerance, insulin sensitivity, and insulin secretion [167].

A wide variety of compounds including hormones, growth factors, neurotransmitters, nutrient and metabolic activators act as extracellular signals that lead to changes in the free cytosolic Ca^{2+} concentration. Calcium signaling is caused by mobilization of Ca^{2+} from internal stores and by well controlled Ca^{2+} influx from the extracellular space. Changes in Calcium influx can result in beta-cell dysfunction; low Ca^{2+} consumption or vitamin D deficiency can change the equilibrium between the extracellular and intracellular beta-cell Ca^{2+}, which can disturb insulin release in response to glucose load [168]. A study has shown that a calcium deficient diet lowers intracellular free calcium, elevates vitamin D, while activating PTH release from the parathyroid gland resulting in improved Ca^{2+} levels in smooth muscle cells [169]. Vitamin D and Ca^{2+} are metabolically related and are considered as important factors in diabetes. Vitamin D maintains intracellular Ca^{2+} homeostasis, and can produce a positive response on insulin activity by stimulating insulin receptor expression and therefore increase insulin response for glucose transport [170], or indirectly by regulating extracellular Ca^{2+} in order to keep normal Ca^{2+} influx. The conclusion derived from a few observational studies suggests an inverse relationship between vitamin D or Ca^{2+} and insulin resistance [171,172]. However, the data came from several randomized trials indicated different results from no effect of extra Ca^{2+} [173,174] or improved [175,176] insulin action by Ca^{2+} supplement. A part of the fat-soluble D-vitamin is “hidden” in the body fat. Therefore, an inverse association between D-vitamin and insulin resistance may only reflect associations with adiposity and insulin resistance.

3.5.2. Calcium in lipid metabolism-related with obesity

Calcium plays critical roles in intracellular processes in adipose tissue and skeletal muscle [177,178] by its action on adipocytes as well as its influence in insulin-stimulated glucose uptake and storage [179]. Calcium modulates inflammatory response and enhances weight loss. Studies in mice have shown that an increase in Ca^{2+}consumption creates a shift in the utilization of energy stores from carbohydrates to fat and a shift in the partitioning of energy from storage to expenditure. A rise in intracellular Ca^{2+} increases the lipogenic gene expressions and thus promoting lipogenesis, and inhibiting lipid breakdown, which results in high triglyceride buildup [180–183]. Mouse studies have highlighted the effect of high Ca^{2+} diets on body weight reduction in energy-restricted aP2-agouti transgenic mice [184]. To offer more compelling evidence, Zemel et al. [181]. used a mice model to demonstrate that transgenic mice expressing agouti gene in adipocytes consuming a high-calcium diet exhibited less body fat buildup, increased fat breakdown, and decreased fat synthesis and storage compared to mice on a low-calcium diet [180]. Thus dietary Ca^{2+} may act on fat breakdown by altering calcitrophic hormones and Ca^{2+} influx into fat cells. Increasing dietary Ca^{2+} suppresses adipocyte intracellular Ca^{2+} and thereby modulates energy metabolism. Independently,

high-Ca^{2+} diets has been found to exert potent effects in reducing body weight and fat pad mass in energy-restricted aP2-agouti transgenic mice [183]. An increase in dietary Ca^{2+} uptake suppresses adipocyte intracellular Ca^{2+} and thereby coordinately regulate lipogenesis and lipolysis [184,185]. The excess buildup of triglyceride results in obese phenotype of dominant yellow mouse mutations [184,185], which overexpress agouti, a physiological calcium agonist and a key enzyme in de novo lipogenesis. Agouti has been shown to stimulate the expression and activity of fatty acid synthase (FAS). Intracellular calcium regulates lipid metabolism by affecting lipolysis, and lipogenesis [182,186], which in turn may affect appetite and energy expenditure. High-Ca^{2+} diet do not effect energy expenditure, and fat breakdown [187]. González and colleagues assessed 797 individuals 35.6% overweight and 43.7% obese to determine the connection between vitamin D level and obesity in a clinic-based sample in Puerto Rico and found that adults with higher BMI, WC, and WHtR showed lower vitamin D levels [188]. Several laboratories have also reported a coherent relationship between adiposity and vitamin D where a rise in adiposity results in low serum 25(OH)D levels [189–191].

3.5.3. Calcium in hypertension

There is sufficient evidence suggesting that dietary Ca^{2+} intake may provide some protection from hypertension [192] and coronary heart disease [193]. Data obtained from clinical, epidemiological and experimental studies show that Ca^{2+} is a key factor in regulating blood pressure; however, this depiction about Ca^{2+} is not all conclusive. Calcium functions in combination with Na^{+}, K^{+}, and Mg^{2+} to provide an ionic balance to the vascular membrane, and vasodilatation. Although many different factors that can contribute to developing hypertension, low Ca^{2+} diets can be a major high risk factor for developing hypertension. Most studies in genetic and experimental models of hypertension on dietary Ca^{2+} have found an inverse relationship between Ca^{2+} intake and blood pressure. Experiments in animal model have shown that addition of dietary Ca^{2+} in the diets lowers blood pressure, and a low Ca^{2+} diets may increase blood pressure [194]. Although the proposed mechanism of calcium action on blood pressure is not well defined several possible mechanisms by which it can affect blood pressure have been proposed review [195]. Some of the suggested mechanisms have linked dietary calcium to its metabolism in vascular smooth muscle as well as changing vascular quality. Also, Ca^{2+} plays a critical role in the functionality of vascular smooth muscle cell and is required for muscle contraction and relaxation in blood vessels [196]; its entry via receptor- and voltage gated calcium channels causes vascular contraction, whereas a drop in its intracellular levels leads to vascular relaxation [194]. Intracellular free ionized Ca^{2+} is under a very tight control by a variety of mechanisms involving several intracellular organelles. Intracellular free calcium is released in response to a variety of soluble and particulate stimuli. The calcium signals are coded either by their amplitude (amplitude modulated, AM), frequency (frequency modulated, FM) or both and are interpreted differently in different chemical context. The calcium “set-point” defined as the resting calcium level of a cell, can determine the outcome of a particular calcium stimulatory or inhibitory signal even though the actual $[Ca^{2+}]i$ change may be the same. $[Ca^{2+}]i$ is regulated by the intracellular calcium stores including ER and mitochondria which buffer and shape the calcium responses and hence its special and temporal effects on cellular functions. More importantly the activities of a number of mitochondrial dehydrogenases, such as pyruvate dehydrogenase, oxoglutarate dehydrogenase and NAD+-isocitrate dehydrogenase that control largely irreversible reactions are sensitive to calcium [197] thus bringing calcium to the full front of metabolic control. The change in Ca^{2+} increases vascular resistance, elevating blood pressure. Thus a diet's related blood pressure lowering effects may involve multiple interacting components.

Effects of dietary calcium on blood pressure are small. According to latest Cochrane database systematic analyses of 16 trials with 3048 participants which assessed the effect of calcium supplementation on blood pressure in normotensive individuals. The authors noted that an increase in Ca^{2+} intake somewhat lowered systolic and diastolic blood pressure in normotensive individuals, indicating a role of Ca^{2+} in inhibiting hypertension. However, how calcium affects blood pressure is not clear yet. More randomized clinical trials that include young individuals may be useful to determine the exact nature of Ca^{2+} effects on blood pressure [198].

We have directly tested the effects of Ca^{2+}, Mg^{2+}, and K^{+} on fat buildup in wild type and fat mutants of *Caenorhabditis elegans* by applying simple feeding techniques as a metric to d quantify the fat levels in worms fed on media containing various levels of dietary salts. We have shown that high Ca^{2+} diets reduce fat buildup in mutant worms [199]. Also, there was an 8–10% low fat buildup in mutant worms fed on high Mg^{2+} diets than those worms fed on normal diets. It has been known that many metabolic effects of K^{+} are modulated and/or amplified by Mg^{2+}. This firm connection has been shown in a study [128] which focused on a likely protective role of Mg^{2+} in insulin resistance; their data also demonstrated a high degree of correlation of K^{+} with insulin sensitivity. As with Mg^{2+} deficient or Mg^{2+} supplement diets we found a similar pattern of gene expression when worms were grown on K^{+} deficient or K^{+} supplement diets. However, there was no change in fat levels of wild-type or mutant worms fed on K^{+} deficient or K^{+} supplement diet. Although Mg^{2+} and K^{+} deficiency frequently occur together both salts have distinct roles in fat storage [199].

4. Strengths

We have summarized the literature on potential dietary salt supplements for obesity, diabetes or other disorders of energy balance. To our understanding this is the first comprehensive systematic review of dietary salts Na^{+}, K^{+}, Mg^{2+} and Ca^{2+} effect on three pathophysiological metabolic syndromes, diabetes, obesity and hypertension. We have covered articles from experimental, epidemiological, clinical, systematic reviews, and other review articles and to put together the present systematic review. This review provides a valuable insight into the role dietary salts play in insulin resistance, obesity and hypertension. At present, there is evidence to support the notion that giving overweight, diabetic and hypertensive individuals a choice of dietary salt supplements may lead to future treatments to lessen the burden of obesity, hypertension and diabetes syndrome which are common and serious human diseases.

5. Limitations

Due to the heterogeneity of the reports cited the study durations and the complex interactions of the dietary salts with each other and other molecules limited the ability to make direct comparisons between salt findings. According to the reviewed studies, there is no consistent or conclusive evidence regarding the optimal intake for, Na^{+}, K^{+}, $Mg2^{+}$ or $Ca2^{+}$ for optimal therapeutic control of metabolic syndromes. We acknowledge that the risk of developing or alleviating metabolic syndromes based on the effects of dietary salts are still limited, partially due to the complexity of the involvement of each salt in many other biological functions. Although we performed a rigorous and robust systematic literature search, there might be unpublished studies we were not aware of. Lastly, bias was inevitable since articles not published in English were not included in the systematic review.

6. Conclusion

Dietary salts are important factors in metabolic disorder. This emphasizes the need to further illuminate the biological mechanisms and pathological processes to which these salts may contribute to normal metabolism. Further, it is crucial to note the importance of dietary salts on human health but it is also critical to identify the mechanisms that illustrate how deficiency or excess of salts may affect metabolism. Revealing these underlying processes is however, essential for identifying the basis of salt specificities in overall process of metabolism. Also, we need to investigate specific salts that may well have quite different effects on fat storage and utilization. There are clearly massive obstacles to overcome in order to have a complete understanding of the salts global molecular network. Questions surroundings salts and their influence on metabolism are large. No single experiment can explain how salt affects human health. But the data obtained from various studies as mentioned in this review offer an approach to identify the problem. To understand the genetic and physiological causes of metabolic diseases as well as their regulation by environmental factors, the dietary habits, physical activity, or the microbiome, should be considered in any study. Animal models are extremely important for investigating genetic causes, pathogenesis, early diagnosis, and therapies for metabolic disorders. In addition, education about dietary salts and their implication on human health need to be improved for both the medical community and the public. Although interest in this area of research continues to grow, the challenge will be to integrate the action of these salts in metabolic disorder.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets during and/or analyzed during the current study is included in the manuscript and is also available from the corresponding author on reasonable request.

Conflict of interest

All authors declare that they do not have competing interest.

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Authors' contribution

Conceived the study and supervision: SH. Data curation: JS. formal analysis CB, JL, YW, SA. Formal analysis and validation: SH, JL, CB, SA, BS. Wrote the original draft: SH. Edit and comment on the manuscript: FAM, RG, JL, SA, CB.

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