Is the association between vitamin D and metabolic syndrome independent of other micronutrients?

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Running title: vitamin D and metabolic syndrome

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Abstract:

The incidence of metabolic syndrome (MetS) has been increasing globally and it is recognized as a major public health problem. Recently, MetS has been linked to vitamin D deficiency; however, the evidence on this association remains inconclusive. This review therefore aims to depict the existing evidence related to MetS and vitamin D deficiency, and examined some of the possible confounders which may affect the association between vitamin D status and risk of MetS.

Earlier studies on the association between vitamin D deficiency and MetS adjusted the effect of some confounders including, age, sex, body mass index, race, physical activity, smoking, alcohol consumption and energy intake. However, these studies failed to consider other potential confounders. There is evidence that vitamin A, zinc (Zn), and magnesium (Mg) play important roles in the activation and function of vitamin D and perform some gene expression. Furthermore, these micronutrients are also related to several components of MetS including glucose intolerance, dyslipidemia and obesity. Thus there could be an interaction between these micronutrients, vitamin D and MetS.

In conclusion, this review highlights the possible interactions of vitamin A, Zn, Mg and vitamin D with MetS and its components. These findings reinforce the need for further well designed studies that take into account all of the potential confounders including other micronutrients like vitamin A, Zn and Mg status to investigate the independent association of vitamin D status with MetS and its components and also to look for possible interactions among other nutrients which may have similar confounding effects.

Introduction

Metabolic syndrome (MetS) is defined as a cluster of biochemical and physiological abnormalities and it is associated with increased risk of developing non-communicable diseases [1]. Despite the significant global effort to control the MetS risk factors, its prevalence has been increasing persistently [2] and it has now been recognized as one of the major public health problems globally [3; 4].

Although the exact causes of MetS have not yet clearly elucidated, several risk factors and unhealthy behaviours, including diet and lifestyle changes have been attributed to this condition. In recent years, the occurrence of MetS has been linked to vitamin D deficiency [5; 6]. However, the present literature on the association between vitamin D deficiency and the incidence of MetS or its components remain inconclusive [7]. For example, some studies have reported inverse association between serum vitamin D level and risk of MetS [5; 6; 8; 9]; while others have failed to demonstrate such association [10-12]. Similarly, the available literature on the findings of the association between serum vitamin D concentration and MetS components are also mixed. Some, but not all, studies reported a significant association between vitamin D deficiency and glucose intolerance [13], lipid profiles including total cholesterol, LDL, HDL and triglyceride [14], blood pressure [15] and obesity [16].

Further, a systematic review and meta-analysis has shown a negative association between blood 25-(OH) vitamin D concentrations and the risk of MetS only in cross-sectional studies but not in longitudinal studies [17]. Although some of the studies examining the association between vitamin D status and MetS have taken into account some potential confounders, the role of other components that were not assessed, is undeniably likely. Among the nutrients, some vitamins or minerals such as vitamin A, Zinc (Zn) and Magnesium (Mg) have a role in vitamin D activation and/or function. They also take part in controlling some of the MetS components including, central obesity, glucose intolerance, dyslipidemia and hypertension and altogether the development of MetS. Thus it is reasonable to expect a possible interaction of these micronutrients in the association between vitamin D and MetS. Although other micronutrients may also have similar interaction effect on the association between vitamin D and MetS, unfortunately there is no data in the current literature.

In order to fulfil this gap, the present review aims to briefly describe the current knowledge of the MetS and vitamin D including the extent of the problem, and subsequently examined some of the possible confounders which may influence the association between vitamin D status and risk of MetS.

Literature search

This review used a number online search engine including, PubMed (MEDLINE), Cochrane Library (Central) and Web of Science to identify the relevant human studies published up to June 2015. First, the literature search was conducted to identify any studies that reported the association between MetS and vitamin D. Second, in order to identify possible confounders among nutrients, the search focused on the literature that investigated the association or interaction between MetS and vitamin D and possible confounders including vitamin A, Zn, Mg, iodine, vitamin K, vitamin C, vitamin E, and calcium. A possible interaction was only reported for vitamin A, Zn, Mg and calcium in previous studies. However calcium has been already assessed as a confounder in the association between MetS and vitamin D. Thus the combination of vitamin D and vitamin A, Zinc or Magnesium were used for the database search. Titles and abstracts were individually reviewed to include relevant articles. Reference lists of selected articles were also searched for other possible related articles. Altogether, only eight human studies published in peer reviewed journals were eligible for the analysis (Table 2).

Metabolic syndrome

The MetS has received much attention in the past decades as it helps to identify the risk of both type-2 diabetes and cardiovascular diseases (CVD) [18; 19]. MetS increases the risk of diabetes mellitus, stroke, coronary heart disease, myocardial infarction and other chronic diseases [20-23]. These diseases are the leading cause of all deaths in both the developed and developing countries [24]. It has also been reported that CVD death and all-cause mortality were higher in MetS participants, even if they were free of diabetes and CVD at baseline [24]. As a consequence of sedentary lifestyles, the population ageing and the increasing prevalence of obesity, the prevalence of MetS has been increasing worldwide [25]. Globally, the reported prevalence of MetS varies between 10% to more than 80% in different populations based on different definitions [26].

Because of the importance of identifying the individuals with MetS, various expert groups/panels have attempted to define diagnostic criteria for MetS. Table 1 shows different definitions of MetS proposed by different expert groups. The first definition of MetS proposed by the World Health Organization (WHO) consultation group which was based on the importance of insulin resistance in diagnosing the MetS [27]. Then the European Group for the Study of Insulin Resistance (EGIR) suggested a modification of WHO definition

which incorporated fasting plasma glucose as an easier method for glucose intolerance [28]. The National Cholesterol Education Program, Third Adult Treatment Panel (NCEP ATP III) definition did not obligatorily required to measure glucose intolerance, rather suggested the presence of any three of the five components: central obesity, raised blood pressure, high triglycerides, low HDL-cholesterol and fasting hyperglycaemia [29]. Finally the International Diabetes Federation (IDF) proposed that central obesity as the most important component of MetS, and thus recommended that the presence of central obesity along with any two of the four additional factors (raised blood pressure, high triglycerides, low HDL-cholesterol and fasting hyperglycaemia) was required to define the MetS [30].

Risk factors of metabolic syndrome

A wide variety of risk factors has been associated with the increased incidence of MetS. Overweight and obesity [31], ageing [32], smoking [33], physical inactivity [34], excess caloric intake [35] and genetics [36] were reported to be the most important risk factors. Other studies reported an association between MetS or its components and dietary factors, including consumption of fat [37], dairy products [38], grains [39], simple sugars [40], salt and alcohol consumption [35]. Furthermore, some minerals and vitamins were also found to be associated with the incidence of MetS. For example, studies have shown an association of MetS or its components with vitamin D [9; 41; 42], calcium [43], vitamin A [44], Zn [45] and magnesium (Mg) [46]. Among these micronutrients, vitamin D is one of the most noticeable nutrients that has recently received much attention worldwide.

Vitamin D

Vitamin D deficiency or insufficiency is a widespread problem in different populations [47-49] and it has been estimated that up to a billion people may be affected globally [50] and thus emphasised as a probable global pandemic in the 21st century [51]. Vitamin D can be synthesised in the skin through exposure to ultraviolet (UV) light from sun (which is a major source of vitamin D) or can be obtained through dietary intake which exerts minor influence to vitamin D status. This form of vitamin D is not biologically active and need to be converted to the active form in the body. First, vitamin D is converted to 25-hydroxy vitamin D [25(OH)D] in the liver by , and then in the kidney it is converted to 1,25-dihydroxy vitamin D [1,25(OH)₂D] which is the active form of vitamin D [52]. Other studies also confirmed that

other tissues such as skin, lymph nodes, pancreas and colon also have 1- α -hydroxylase enzyme and can produce [1,25(OH)₂D] [53]. Because 1,25(OH)₂D is formed in some tissues and it has a short half-life and it is affected by the parathyroid hormone, calcium and phosphate concentrations, serum 1,25-dihydroxy vitamin D level is not a good indicator of vitamin D status [54]. To date, serum 25(OH)D is considered to be the best measure of body vitamin D status [55]. Although there is no consensus on vitamin D sufficiency levels, vitamin D deficiency has been defined by most experts as serum 25(OH) vitamin D level lower than 50 nmol/l (20 ng/ml) [56-58]. However, some other studies proposed a cut-off point of below 80 nmol/l (32 ng/ml) to describe vitamin D insufficiency [59].

As vitamin D synthesis in the skin is the most important source of this vitamin, any factor that reduce the exposure of sunlight or decrease the concentrations of 7-dehydrocholesterol will cause vitamin D deficiency. Older individuals who have lower 7-dehydrocholesterol levels [60] and lower ability to synthesize vitamin D in the skin [61], are more susceptible to vitamin D deficiency. Consequently, in western countries, 40–100% of elderly people are vitamin D deficient [62; 63]. High prevalence of vitamin D deficiency is also observed among obese individuals, may be because of trapped vitamin D in subcutaneous fat [64; 65] or lower sunlight exposure and outdoor activity [63; 66]. Urbanisation and westernized lifestyles including, indoor lifestyles, sun prevention strategies and clothing style, as well as skin pigmentation inhibit vitamin D production in the skin [67].

Vitamin D functions

The best known classical role of vitamin D is related to calcium metabolism and maintaining bone health [50]. For this function, vitamin D interrelates with its nuclear receptor in the related tissues including bone, intestine and kidney [68-70]. The non-genomic function of vitamin D, which have been described in many cell types, include changes in the concentrations of intracellular calcium [71]. It has been shown that even in individuals with genetic defects of vitamin D metabolism, vitamin D is essential for active calcium absorption. Alternatively bone mineralization can take place by high doses of calcium [72]. In addition, vitamin D produces biological reactions in more than 30 target tissues and can generate genomic biological responses and regulates more than 200 genes, including those related to insulin, renin and cytokines [73]. In addition, the 1- α -hydroxylase enzyme [74] and 1,25(OH)₂D nuclear receptors, known as vitamin D receptors (VDR), have been found in a

large number of different cells and organs including skin, osteoblasts, brain, gonads, immune cells, vascular endothelial cells, pancreas, and lymphocytes [75-77].

Vitamin D performs its hormone-like functions to adjust its target genes via binding to VDR [78]. The vitamin D function is mediated through a single receptor which acts by vitamin D-responsive elements (VDREs) which are repeated sequences of nucleotides. The 3' arm of these sequences bind the VDR and the 5' arm binds the retinoic acid X receptor (RXR) [79]. VDR, in cooperation with RXR, forms a heterodimer at the VDREs [80]. Simultaneously, VDR binds other proteins and an activator required for the gene transcription [81] which is related to several functions. Moreover, different genes are selective for the co-regulator (inhibitory or stimulatory) which with VDR heterodimer regulates their transcription [82].

It has previously been reported that individuals living at higher latitudes, and having lowest exposure to sunlight, are at a higher risk of various chronic diseases [83]. Recent studies have indicated that the risk of all-cause and cardiovascular related mortality are higher in individuals with low serum vitamin D levels [10; 84]. Low vitamin D status is also associated with diabetes, hypertension, atherosclerosis, congestive heart failure, myocardial infarction, cardiovascular risk, stroke, kidney dysfunction, infections and cancers [8; 50; 55; 85-96]. However, most recently, Theodoratou et al [97] have carried out an umbrella review of the evidence across systematic reviews and meta-analyses of observational studies and randomised controlled trials that were related to vitamin D and various diseases and failed to draw a firm conclusion about the beneficial effects of vitamin D and health outcomes [97].

Vitamin D and Metabolic Syndrome

Several epidemiologic studies have reported an inverse association between MetS and serum 25 hydroxy vitamin D concentrations [9; 41; 42]. In addition, other studies have shown that individuals with vitamin D deficiency were up to three times more at risk of developing MetS than individuals with normal vitamin D status [92; 98]. As MetS is defined by its components, any association between vitamin D deficiency and MetS components can influence the association between vitamin D and MetS. As indicated earlier, studies have found an inverse association between vitamin D status and diabetes [8; 99]. It has been suggested that vitamin D, via its effect on intracellular calcium [100], is associated with inflammation, pancreatic beta cell function and insulin resistance [101]. Moreover, adipose tissues and skeletal muscles, which are related to peripheral insulin sensitivity, have VDR [102; 103]. Pancreatic β -cells and the insulin gene promoter also have a VDR section [104],

which could explain the role of vitamin D on glucose homeostasis. Adequate vitamin D status has also been found to be associated with blood pressure, probably by its role on the down-regulation of renin and angiotensin and therefore, reducing blood pressure [105]. 1,25(OH)₂D also suppress the production of renin-angiotensin system components in pancreatic islets [106]. Furthermore, the presence of VDR in vascular smooth muscles and endothelial cells may justify the vascular effect of vitamin D [107]. Vitamin D deficiency was also found to be associated with obesity [86]. It has been proposed that vitamin D may work with calcium to increase postprandial fat oxidation [108] or may inhibit adipogenesis because of its role on gene expression [109]. It has also been proposed that obese individuals need more vitamin D for stronger bones to support their greater weight, or may have lower vitamin D production as a consequence of clothing habits or restricted outdoor activity and less exposure to UVB [110].

Although several investigations accepted vitamin D deficiency as a risk factor for MetS [42; 92; 98; 111-118], several studies could not demonstrate any significant association [9-12; 42; 115; 119; 120]. The discrepancy between studies on the association between vitamin D and MetS or its components has been justified by population differences in exposure to UVB irradiation, residential place, skin exposure to sunlight, different dietary intake and genetics differences [119]. Although some of these studies controlled possible confounders including, age, sex, BMI, race, physical activity, smoking, alcohol consumption, and energy intake, the role of other confounders are irrefutable. For example, vitamin A, Zn, Mg, iodine, vitamin K, vitamin C, vitamin E, and calcium are related to vitamin D, MetS or its components. Based on the current literature, vitamin A, Zn, and Mg are related to the activation and function of vitamin D as well as MetS and/or its components but these micronutrients were not considered as possible confounders in previous studies. Therefore, it is likely that these micronutrients could act as potential confounders while examining the association between vitamin D and MetS and/or its components. Table 2 summarizes the human studies investigating the interaction between vitamin D and other nutrients. The following section will describe the findings of available literature which examined the possible links between these micronutrients and vitamin D and MetS.

Possible role of vitamin A

Vitamin A deficiency is a major public health problem in low income countries [121]. The main cause of vitamin A deficiency is inadequate dietary intake of vitamin A over a long

period which leads to inefficient body stores and thus unable to meet the physiological needs [122]. Retinol, retinoic acid (RA), or pro-vitamin A (β -carotene and other carotenoids) are the sources of vitamin A in the diet [123].

It has been reported that the plasma levels of vitamin A were inversely associated with MetS prevalence [124]. It has also been shown that plasma carotenoids concentrations were significantly lower in MetS participants when compared with healthy individuals and the serum carotenoids levels were significantly reduced with an increased number of MetS components [125-127]. Antioxidant activity of carotenoids that protect against oxidative stress has been suggested as a possible mechanism to reduce MetS [125]. In addition, vitamin A intake was found to be inversely associated with several biochemical and anthropometric measurements (body weight, BMI, waist circumference and waist hip ratios) that were linked to MetS manifestations [44].

Vitamin A along with vitamin D stimulates production of proteins through some gene expression [128]. Binding of RA to nuclear RA receptors (RARs) and retinoid X receptors (RXRs) forms heterodimers which regulate the expression of specific target genes [128]. This complex also supports VDR signalling and prevents the degradation of vitamin D [129]. To regulate the gene expression and transcription, RXR requires to form a heterodimer complex with VDR (VDR:RXR heterodimer) [130] (Figure 1). Synergistic or antagonistic interactions between vitamin A and vitamin D have been reported in in-vitro studies [131]. It has also reported that higher vitamin A intakes cause more prevalent and severe osteoporosis [132]. A high dose of retinol as an antagonist of vitamin D could cause osteoporosis, rickets and non-bony vitamin D related diseases [133]. In human studies, it has been demonstrated that retinol antagonizes the serum calcium response to vitamin D [134]. The interaction between vitamin A and vitamin D has confirmed by other studies [135; 136].

Thus vitamin A may act as a potential confounder while examining the association between vitamin D and MetS and hence it is important to take its effect into account in order to investigate an independent association of vitamin D and MetS.

Possible role of Zinc

Zinc (Zn) deficiency is one of the major mineral deficiencies throughout the world [123]. The Food and Agriculture Organization (FAO) reported that around 50 percent of the world's population are at a risk of inadequate intake of Zn [137]. The catalytic role of Zn has been discovered in many enzymes and around 300 Zn metalloenzymes have been found [138].

Zn plays an essential role in antioxidant system including, glutathione peroxidase, superoxide dismutase, and catalase [139] and decrease production of inflammatory cytokine through Zn-finger protein regulation [140]. Thus Zn could be related in the pathophysiology of the MetS [141]. The association between Zn and MetS components is contradictory. There are studies which reported that surplus Zn, via the renin-angiotensin system, might increase blood pressure [142], and Zn supplementation reduces plasma HDL-C concentrations [143]. However, others recommended Zn supplementation as a safe intervention to decrease the risk of MetS [144]. Moreover, Zn affects the body fat deposition and the insulin activity [145]. It has also been connected with pancreatic β -cells insulin secretion, and so is associated with diabetes and obesity [146]. Zn deficiency and its metabolic disorders are also associated with the pathogenesis of several chronic diseases [147].

Zn is a vital component of steroid hormone receptors and is bound with the DNA binding domains by zinc-finger proteins. Removal of Zn from zinc-finger proteins changes the structure, and cause dysfunction and probably degradation of the proteins [123]. Intracellular Zn binds with VDR and influences the activity of vitamin D dependent genes [148]. Zn also improves the effect of vitamin D on the activity of alkaline phosphatase and DNA synthesis [149]. Zn deficiency causes bone calcification disorders which is comparable with vitamin D deficiency [150]. It has also been described that Zn enhances the activity of vitamin D dependent promoters [151]. In human studies, Zn supplementation particularly in the presence of vitamin D increase bone mass [152].

Overall, Zn appears to help in various functions of vitamin D in the body, and may also be related to some components of MetS. Thus, Zn status in individuals could be very important factor when examining the association between vitamin D status and the risk of MetS.

Possible role of Magnesium

Mg deficiency has been frequently reported in patients with hypertension [46], dyslipidemia [153], diabetes [154] and cardiovascular diseases [155]. Mg plays important roles in a wide range of biologic reactions and is responsible for more than 300 essential metabolic responses [156; 157]. Mg is connected with calcium homeostasis [158] and is also associated with the metabolism of vitamin D [159]. It is essential for the binding of vitamin D with its carrier protein thus helps in the transportation of vitamin D in the body and is necessary for the conversion of inactive vitamin D into active forms [25(OH) D and 1,25(OH)₂D] in the liver and kidney respectively [160; 161]. Earlier investigations found a higher prevalence of Mg

insufficiency or deficiency in individuals with lower concentration of serum vitamin D [162]. Other studies revealed that Mg deficiency is associated with reduction in the active form of vitamin D [1,25(OH)₂D] and causes resistance to pharmacological doses of vitamin D [159] and is related to vitamin D resistant rickets [161]. Conversely, Mg supplementation reduces the resistance to vitamin D treatment for rickets [160]. Additionally, a positive association between vitamin D levels and serum Mg has been reported in human studies [163-165]. Vitamin D supplementation was also associated with increased serum Mg concentration in obese individuals [166].

On the other hand, Mg deficiency and/or low Mg intakes are associated with MetS [167] and its components including insulin resistance [168], diabetes mellitus [169], hypertension [46], dyslipidemia [153] and cardiovascular diseases [155]. It has been suggested that Mg intake and intracellular Mg influence insulin secretion [170; 171] and insulin function [172] through its effect on calcium homeostasis, stimulation and transcription of some enzymes and nuclear proteins and oxidative stress [46]. Mg as a calcium antagonist, can inhibit the intracellular calcium mobilization [173], increase sodium excretion in urine and control blood pressure [173]. Mg also acts as a co-factor for several enzymes affecting lipid metabolism [174] and can decrease the absorption of fatty acids and cholesterol in intestine by forming an un-absorbable soap and decrease energy intake which may prevent obesity [175].

A recent study also showed a possible interaction between serum vitamin D, Mg intake and mortality [165]. Because of the association between Mg deficiency and MetS, and the effect of Mg on the serum level of vitamin D and its activation, a potential interaction between vitamin D, Mg and MetS is conceivable.

Strength and limitations

While this review revealed a complex interaction between vitamin D, MetS and other micronutrients, the major limitation is that there are limited literatures that have reported this interaction. However, the strength of this study is that it is the first review that collated the available documents to address the interaction of other micronutrients with vitamin D and MetS.

Conclusion

Despite the increasing evidence on the importance of vitamin D in the prevention of metabolic diseases, presently there is significant inconsistency in the findings of the available literature regarding the association between vitamin D status and MetS, which made it difficult to draw a firm conclusion. This review also highlights possible interactions of vitamin A, Zn, Mg and vitamin D with MetS and its components. Finally, this review reinforces the need for further studies by controlling the confounding effects of other nutrients to confirm the association between vitamin D status and MetS and its components and also to look for possible interactions among other nutrients which may have similar confounding effects.

Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

H.K. searched and designed the concept of study and prepared the draft manuscript. F.A. and N.S. has provided guidance on the study design and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Table 1: Metabolic syndrome definitions

	WHO (1999)	EGIR (1999)	NCEP ATP III	IDF
Definitions	insulin resistance together with two or more of the following:	Insulin resistance or impaired fasting glucose (IFG) plus two of the following:	Three or more of the following five risk factors:	Central obesity plus 2 other features
Fasting plasma glucose	—	≥ 6.1 mmol/l (110 mg/ dl) but non-diabetic	≥ 5.6 mmol/l (100 mg/ dl)	≥ 5.6 mmol/l (100 mg/ dl) or diagnosed type 2 diabetes
Central obesity	Men: waist–hip ratio > 0.90 Women: waist–hip ratio > 0.85 and/or BMI > 30 kg/m ²	Men: waist circumference ≥ 94 cm Women: waist circumference ≥ 80 cm	Men: waist circumference > 102 cm Women: waist circumference > 88 cm	Men: waist circumference ≥ 94 cm , Women: waist circumference ≥ 80 cm *
Blood pressure	$\geq 140/90$ mmHg	$\geq 140/90$ mmHg or treatment	$\geq 130/ 85$ mmHg	or BMI > 30 kg/m ² $\geq 130/85$ mmHg or treatment
Triglycerides	≥ 1.7 mmol/l (150 mg/ dl)	> 2.0 mmol/l (178 mg/ dl)	≥ 1.7 mmol/l (150 mg/ dl) or treatment	≥ 1.7 mmol/l (150 mg/ dl) or treatment
HDL-cholesterol	Men: < 0.9 mmol/l (35 mg/ dl) Women: < 1.0 mmol/l (39 mg/ dl)	< 1.0 mmol/l (39 mg/ dl) or treatment	Men: < 1.03 mmol/l (40 mg/ dl) Women: < 1.29 mmol/l (50 mg/ dl)	Men: < 1.0 mmol/l (39 mg/ dl) Women: < 1.3 mmol/l (40 mg/ dl) or treatment

Table 2: Human Studies mentioned the interaction between vitamin D and other nutrients

Authors (year), Country	Participants	Study design	Results and comments
Vitamin A and vitamin D			
Schmutz et al. 2015, USA	15,998 adults	Cohort	Negative associations between serum vitamin D and risk of death was reported only among individuals with serum retinylesters <7.0 µg/dL. A possible interaction between serum vitamin D and vitamin A levels is probable.
Cheng et al. 2014, USA	14,254 50-69 years	Case-Control	Vitamin D supplementation was associated with a lower risk of total lung cancer among individuals who had vitamin A intake ≥1,500 µg/day. Vitamin A may support vitamin D in cancer prevention.
Johansson et al. 2001, Sweden	9 healthy subjects	Intervention	Intake of vitamin D plus retinal weakened the calcium response to vitamin D. Vitamin A intake antagonizes the quick intestinal calcium response to vitamin D in man.
Zinc and vitamin D			
Ekbote et al. 2015, India	31 children	Intervention	Adding zinc to calcium and vitamin D supplementation increased the bone mineral content. Zinc supplementation particularly in the presence of vitamin D increase bone mass.
Magnesium and vitamin D			
Gandhe et al. 2013, India	30 healthy and 30 type 2 diabetics	Case-Control	A positive association between vitamin D and magnesium levels was detected. Vitamin D has the potential to decrease insulin resistance and also can affect magnesium status.
Al-Daghri et al. 2014, Saudi Arabia	126 adult	Intervention	Magnesium levels significantly increased after the vitamin D supplementation. Vitamin D supplementation increases the serum level of magnesium
Deng et al. 2013, USA	12157 adults NHNES study	Cross-sectional and Cohort	High Mg intake was diminished the risk of vitamin D. A possible metabolic interaction between vitamin D and deficiency magnesium is stated.
Farhanghi et al. 2009, Iran	82 women (17-50 years)	Intervention	Vitamin D supplementation increased serum Magnesium level in obese individuals. In obese people vitamin D can modify low serum Magnesium levels

Figure 1: function of vitamin D and vitamin D in gene expression