

The Clinical Use of Magnesium in the Prevention and Management of Insulin Resistance and Type 2 Diabetes

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Introduction

The incidence of type 2 diabetes mellitus and insulin resistance is reaching epidemic proportions both in Australia and globally. Type 2 diabetes and insulin resistance are primarily conditions related to lifestyle in particular lack of physical activity and excessive calorie intake. Those with type 2 diabetes and insulin resistance have been found to be deficient in several minerals including magnesium. There is evidence that magnesium may play a role in the prevention and management of insulin resistance and type 2 diabetes.

Diabetes mellitus

Diabetes mellitus is a category of metabolic diseases resulting from defects in the secretion of insulin, the action of insulin, or both. Diabetes is characterised by chronic hyperglycaemia leading to long-term complications relating to tissue damage and subsequent organ failure. The kidneys, nerves, eyes, heart, and blood vessels are particularly involved. There are several pathogenic processes involved in the development of diabetes. These pathologies range from cellular mediated autoimmune destruction of the β -cells of the pancreas with consequent insulin deficiency as observed in type 1 diabetes, to abnormalities that result in resistance by the body to the action of insulin on target tissues despite adequate production. The basis of the aberrations in protein, carbohydrate and fat metabolism in diabetes is inadequate insulin action on target tissues. Deficient insulin action results from the insufficient secretion of insulin and/or abnormal tissue responses to insulin at one or many locations in the intricate pathways of insulin action. Impaired secretion of insulin and deficiencies in its action frequently coexist in the same patient, and it may not be evident which irregularity, if either exclusively, is the fundamental cause of the hyperglycaemia (American Diabetes Association, 2006).

The course of diabetes is progressive. Symptoms due to chronic hyperglycaemia include polyuria, glycosuria, polydipsia, polyphagia, weight loss, blurred vision and impaired immune function. Numerous long-term complications can also occur. These include peripheral neuropathy with the risk of foot ulcers and amputations, retinopathy with potential vision loss, nephropathy with potential renal failure, and autonomic neuropathy leading to cardiovascular and gastrointestinal symptoms, and sexual dysfunction. Those with diabetes have an increased incidence of cardiovascular, peripheral arterial and cerebrovascular disease including a high frequency of hypertension and irregularities related to lipid metabolism. Immune function may also be impaired and infections are common (Anderson, 2001, American Diabetes Association, 2006).

The majority of cases of diabetes fall into two broad etiological groups: type 1 diabetes mellitus and type 2 diabetes mellitus. In type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing type 1 diabetes can frequently be identified by evidence of an autoimmune pathologic process occurring in the pancreas and by genetic markers. In type 2 diabetes, the cause is a combination of resistance to the action of insulin action and an inadequate secretion of insulin. In type 2 diabetes, the degree of hyperglycaemia is frequently sufficient to cause pathologic and functional changes in target tissues, without resulting in obvious clinical symptoms and may be present for an extended period of time prior to diagnosis. Type 2 diabetes is by far the most prevalent type of diabetes with rates increasing globally (American Diabetes Association, 2006).

Epidemiology

A number of studies have been conducted in an attempt to estimate the current global incidence of diabetes and to predict the rising global incidence of diabetes. The number of people with diabetes is rising due to the increasing prevalence of obesity, physical inactivity, population growth, urbanisation and ageing. According to figures produced by the World Health Organisation (WHO) in 2000, the global incidence of diabetes in was estimated to be 171 million. This figure is expected to increase to 366 million by 2030. In 2000 the global prevalence of diabetes for all age groups was estimated to be 2.8% and this is predicted to increase to 4.4% by 2030 (Wild 2004). Most epidemiological data do not differentiate between type 1 and type 2 diabetes however it is estimated that between 90 and 95% of those with diabetes have type 2 diabetes (Shaw, 2003, American Diabetes Association, 2006).

According to the most recent study of diabetes prevalence in Australia, the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) conducted in 2000, the prevalence of diabetes in those age 25 and older was 7.5%: 8.0% for males and 7.0% for females. It was estimated that about 940 000 people over the age of 25 have diabetes. The incidence of diabetes in Australia has increased and continues to increase. The most recent estimates of the national prevalence prior to the AusDiab study from the 1995 ABS National Health Survey determined that 430 700 Australians were aware of having diabetes. According to global predictions conducted by the WHO in collaboration with the International Diabetes Institute it was estimated that by the year 2010 1.23 million people in Australia will have diabetes. In addition to those with diabetes the AusDiab study found that the prevalence of those with impaired glucose tolerance (IGT) was 10.6% and those with impaired fasting glucose (IFG) was 5.7%. See Table 1 for a Classification of Glucose Tolerance Status as defined by the AusDiab Study. AusDiab found that only about half of those found to have diabetes were aware of having the condition and that for every known case of diabetes there was one newly diagnosed case: that is the actual prevalence of diabetes is double that self-reported (Dunston et al., 2001).

Table 1: Classification of Glucose Tolerance Status

Plasma glucose (mmol/l)

Classification Fasting 2-hr

Diabetes > 7.0 or > 11.1

IGT < 7.0 and 7.8 – 11.0

IFG 6.1 – 6.9 and < 7.8

Normal < 6.1 and < 7.8

Adapted form: Dunston et al. (2000)

In addition to the increasing prevalence of type 2 diabetes in the adult population, the incidence is also increasing in children and adolescents. A recent study conducted in New Zealand found that the incidence of type 2 diabetes increased from 1.8% in 1996 to 11% in 2002. The mean age of these adolescent diabetics was 15 years old and the mean body mass 34.6kg/m². In addition, 85% had dyslipidaemia, 58% increased albumen excretion rates, and 28% systolic hypertension (Hotu et al., 2004).

Classification of Diabetes Mellitus

The various forms of diabetes have been classified and are predominantly etiologically-based.

Type 1 Diabetes Mellitus

This form of diabetes was previously encompassed by the terms 'insulin-dependent diabetes mellitus', 'type 1 diabetes' or 'juvenile-onset diabetes'. Type 1 diabetes usually results from a cellular-mediated autoimmune destruction of the β -cells of the pancreas. The rate of β -cell destruction is quite variable, usually being rapid in infants and slower in adults. During the latter stage of the disease, the islets of Langerhans contain no or few functional β -cells resulting in little or no insulin secretion. Without treatment the body develops systemic metabolic acidosis and hyperglycaemia and glucosuria lead to electrolyte and fluid imbalances leading to coma and death. Markers of β -cell immune destruction including markers of islet cell

autoantibodies and autoantibodies to insulin, glutamic acid decarboxylase and the tyrosine phosphatases are present in 85-90% of those with type 1 diabetes when fasting diabetic hyperglycaemia is initially detected. The peak incidence of autoimmune type 1 diabetes occurs during childhood and adolescence however it may occur at any age (Rubin & Farber, 1988, American Diabetes Association, 2006).

There is a genetic predisposition to the autoimmune β -cell destruction; however environmental factors, which are still poorly defined, may also play a role. Individuals who present with type 1 diabetes are not usually obese however the existence of obesity does not preclude them from the diagnosis. Those with this form of diabetes are reliant on insulin for survival and likely to develop ketoacidosis if poorly controlled. Individuals with type 1 diabetes are also prone to other autoimmune disorders such as coeliac disease, Graves' disease, Hashimoto's thyroiditis, Addison's disease, autoimmune hepatitis and myasthenia gravis (American Diabetes Association, 2006).

Some forms of type 1 diabetes are idiopathic having no known aetiologies. Some patients have permanent insulinopaenia and are prone to ketoacidosis, but have no markers of β -cell auto-immunity (Mc Larty 1990). This accounts for a minority of patients with type 1 diabetes, mostly of African or Asian descent (American Diabetes Association, 2006).

Type 2 Diabetes Mellitus

The term 'type 2 diabetes' encompasses what was previously termed 'non-insulin-dependent diabetes mellitus' or 'adult-onset diabetes' (American Diabetes Association, 2006). Type 2 diabetes is the most common form of diabetes. It is a complicated metabolic disorder characterised by hyperglycaemia and associated with a relative deficiency of insulin secretion, along with a reduced response of target tissues to insulin known as insulin resistance (Shaw & Chisholm, 2003).

Individuals with type 2 diabetes, at least initially and often for their lifetimes do not require insulin for survival. Those with this form of diabetes are not usually insulin-dependent or prone to ketosis however they may use insulin for symptomatic treatment of persistent hyperglycaemia and can develop ketosis in particular circumstances such as during stress or infections. Type 2 diabetes results from a combination of genetic, environmental and behavioural factors (American Diabetes Association, 2006).

Most patients with type 2 diabetes are overweight or obese, and obesity itself causes or aggravates insulin resistance (Campbell & Carlson, 1993). Those who are not classified as obese by traditional weight criteria such as body mass index, may have increased abdominal adiposity (Kissebah et al., 1982) or high levels of skeletal muscle fat (Goodpaster et al., 2003).

Other factors likely to influence the likelihood of developing type 2 diabetes include lack of physical activity, age and poor nutrition. Type 2 diabetes is more common in individuals with a family history of the disease and certain ethnic groups are more prone to this condition than others. It occurs more frequently in women with a history of gestational diabetes or polycystic ovarian syndrome and in individuals with hypertension, dyslipidaemia, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) (American Diabetes Association, 2004).

Gestational Diabetes

Diabetes or any degree of glucose intolerance with onset or first recognition occurring during pregnancy is known as gestational diabetes. Gestational diabetes occurs in 1 - 14% of pregnant women, depending on the population studied. Women already diagnosed with diabetes who subsequently become pregnant are not included in this diagnosis. It does not exclude the possibility that undiagnosed glucose intolerance or diabetes antedates or occurs at the time of pregnancy. The definition applies regardless of whether or not insulin is used for treatment or whether dysglycaemia continues after pregnancy. In the first trimester and the first half of the second trimester, fasting and postprandial glucose levels are normally lower than those of non-

pregnant women. Elevated levels during this period may reflect the presence of diabetes, which has antedated pregnancy. Decreased glucose tolerance occurs normally during pregnancy, predominantly in the third trimester (World Health Organization, 1999, American Diabetes Association, 2006). Gestational diabetes usually resolves following after childbirth however the risk of developing type 2 diabetes, particularly within five years is greatly increased (Kim et al, 2002).

Other Specific Types

There are a number of other specific types of diabetes mellitus which have other etiologies. These are less common and often secondary to other conditions. These types of diabetes may be related to diseases of the pancreas, endocrine diseases, drugs or chemicals, infections and genetic syndromes (World Health Organization 1999).

Table 2: Summary of Etiological Classification of Diabetes Mellitus
Types of Diabetes Mellitus

Type 1 Diabetes Mellitus:

β -cell destruction leading to or due to absolute deficiency of insulin

• Auto-immune

• Idiopathic

Type 2 Diabetes Mellitus:

May range from predominantly insulin resistant with relative deficiency in insulin secretion to predominantly secretory deficiency with or without insulin resistance

Gestational Diabetes:

Diabetes with onset during pregnancy

Other specific types:

• Genetic defects of β -cell function, e.g. Chromosomal 20, HNF4a (MODY1)

• Genetic defects in insulin action, e.g. Type A insulin resistance, Leprechaunism

• Pancreatic damage or disease, e.g. pancreatitis, trauma, infection, cancer, cystic fibrosis

• Endocrinopathies, e.g. acromegaly, Cushing's syndrome, hyperthyroidism, haemachromatosis

• Drug or chemical-induced, e.g. β -adrenergic agonists; glucocorticoids, nicotinic acid, thyroxine, thiazides

• Infections, e.g. congenital rubella, cytomegalovirus

• Uncommon forms of immune-mediated diabetes, e.g. insulin auto-immune syndrome

• Other genetic syndromes, e.g. Down's syndrome, Huntington's chorea, Prader-Willi syndrome

Adapted from: World Health Organization. (1999) and American Diabetes Association, (2006).)

Insulin Resistance

A reduced response of target tissues to insulin is known as insulin resistance and is a common feature of type 2 diabetes. Reaven (1998) defines insulin resistance as resistance to insulin-mediated glucose disposal and compensatory hyperinsulinaemia. Insulin resistance is frequently associated with a number of diseases, including hypertension, obesity, polycystic ovarian syndrome and type 2 diabetes. Insulin resistance and the metabolic syndrome are not synonymous; however resistance to insulin- greatly increases the risk of developing the various abnormalities related to the metabolic syndrome. The combination of insulin resistance, dyslipidaemia, hypertension, and obesity form the four components of what has been described as the 'metabolic syndrome'. The metabolic syndrome is known to be a strong determinant of type 2 diabetes (Reaven 2002). Insulin resistance is present in the majority of individuals with poor glucose tolerance or type 2 diabetes (Reaven 1998). Most patients with insulin resistance are however overweight or obese. Abdominal obesity in particular may increase the degree of insulin resistance compared to the effect of general obesity however according to Reaven (2002), the strength of the association between insulin resistance and abdominal obesity, compared to

that with general obesity, may be exaggerated. Not all overweight or obese individuals are insulin resistant, nor are all those who are insulin-resistant overweight (Reaven 2002). Whether obesity results in insulin resistance or insulin resistance causes obesity remains unknown. In some studies baseline fasting insulin levels are associated with future weight gain, suggesting that hyperinsulinaemia results in increased obesity (Odeleye, 1997, Johnson et al., 2001). Table 3 summarises the abnormal changes that are likely to occur in individuals with insulin resistance and compensatory hyperinsulinaemia. In addition to the changes listed in Table 3, there is evidence that non-alcoholic steatohepatitis (Chitturi et al., 2002), benign p

Table 3: Abnormalities Associated with Insulin Resistance/Hyperinsulinaemia

Abnormalities Associated With Insulin Resistance/Hyperinsulinaemia

Glucose intolerance

Impaired fasting glucose

Impaired glucose tolerance

Abnormal uric acid metabolism

 Plasma uric acid concentration

 Renal uric acid clearance

Dyslipidaemia

 Triglycerides

 HDL-cholesterol

 LDL- cholesterol

 Postprandial lipaemia

Haemodynamic

 Sympathetic nervous system activity

 Renal sodium retention

 Blood pressure (about 50% of individuals with hypertension are insulin resistant)

Haemostatic

 Plasminogen activator inhibitor-1

 Fibrinogen

Endothelial dysfunction

 Mononuclear cell adhesion

 Plasma concentration of cellular adhesion molecules

 Plasma concentration of asymmetric dimethyl arginine

 Endothelial-dependent vasodilatation

Reproductive

Polycystic ovarian syndrome

Adapted from: Reaven (2002)

Risk Factors

There are a number of factors that put people at risk of insulin resistance and type 2 diabetes. Some of these factors are well-known and accepted by medical practitioners whereas others are less well-known and more controversial. The genetic, environmental and metabolic factors responsible for insulin resistance and pancreatic -cell failure and the precise sequence of events leading to the development of type 2 diabetes are not yet fully understood.

The risk of developing type 2 diabetes increases with age. It is more common in individuals with a family history of the disease and among certain racial or ethnic groups. Those with conditions such as hypertension, dyslipidaemia or impaired glucose tolerance are also more likely to develop the condition. It occurs more frequently in women with a history of gestational diabetes or with polycystic ovarian syndrome (American Diabetes Association, 2004). Other risk factors include obesity (Van Itallie 1985), lack of physical activity (Manson et al., 1991), a diet low in fibre and high glycaemic foods (Salmeron et al., 1997). Smoking may also be associated with increased risk (Sairenchi 2004). Table 4 represents a summary of established risk factors as proposed by the ADA.

According to Bloomgarden (2002) in an article summarising presentations at the American

Diabetes Association annual meeting in 2002, other established risk factors include pregnancy, drugs, and endocrine and monogenic syndromes. In addition to these established risk factors other less established risk factors are emerging. These include genetic factors, the foetal environment, inflammation, dietary macronutrients, as well as more recently discovered risk factors such as liver disease, micronutrient intake, stress and depression, abnormal lung function with sleep apnoea, and endothelial dysfunction. Individuals with hepatitis C are almost four times more likely to develop diabetes. The mechanism however is yet to be defined and according to Mehta et al., (2000) either hepatitis C could cause diabetes, diabetes could increase risk of hepatitis C, or both could be caused by another underlying factor.

Table 4: Established Risk Factors for Type 2 Diabetes

Established Risk Factors for Type 2 Diabetes

- Age 45 years
- Overweight (BMI ≥ 25 kg/m²)
- Family history of diabetes
- Lack of exercise or physical inactivity
- Race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans and Pacific Islanders)
- Previously identified IFG or IGT
- History of Gestational Diabetes Mellitus or delivery of a baby weighing > 4 kgs
- Hypertension ($\geq 140/90$ mmHg in adults)
- HDL cholesterol ≤ 5 mg/dl (0.90 mmol/l) and/or a triglyceride level ≥ 250 mg/dl (2.82 mmol/l)
- Polycystic ovary syndrome
- History of vascular disease

Adapted from: American Diabetes Association (2004)

Although obesity is considered to be the primary risk factor for type 2 diabetes and insulin resistance, diet including nutrient intake may also play a key role independent of adiposity. Animal studies have demonstrated that a high fructose diet affects insulin action in muscle and liver of rats leading to poor glycaemic control and insulin resistance (Bezzera et al., 2000). However according to a review of over 13 human studies of the effects of dietary sucrose or fructose on insulin sensitivity results were inconsistent (Daly, 2003). Elevated iron stores are positively associated with the prevalence of insulin resistance and type 2 diabetes (Jehn et al., 2004, Jiang et al., 2004). Deficiencies of the minerals magnesium chromium and zinc may also be risk factors as low levels of these minerals are associated with poor sensitivity to insulin (Bloomgarden 2002).

The relationship between stress and disease is now apparent and accepted following numerous studies in the field of health psychology, specifically psychoneuroimmunology. A relationship between stress and abdominal obesity and type 2 diabetes has been proposed. Increased levels of cortisol are associated with obesity, in particular with abdominal obesity. Although the mechanism has yet to be fully elucidated, it appears to be connected to the hypothalamic-pituitary-adrenal gland axis and related endocrine pathways (Bjorntorp & Rosmond, 2000). Patients with sub-clinical Cushing's syndrome are frequently overweight and insulin resistant suggesting an association between high cortisol levels, adiposity and diabetes (Catargi et al., 2003). There is a strong negative relationship between stress-related cortisol secretion and insulin growth factor, testosterone, and HDL cholesterol. Strong, consistent relationships between cortisol and obesity parameters (body mass index, waist-hip ratio), metabolic variables (insulin, glucose, triglycerides, and total and LDL cholesterol) as well as haemodynamic variables blood pressure and heart rate) have also been found (Rosmond et al., 1998). Waist-hip ratio is also associated with symptoms of depression, anxiety and associated sleep disturbances, as well as psychosomatic symptoms and dissatisfaction. Rosmond et al., (1996) suggest increased secretion of cortisol result in directing storage fat to central adipose tissue.

Magnesium

Magnesium is the fourth most abundant cation in the human body and the second most abundant

in the intracellular fluid. A 70kg adult has about 2000 mEq of magnesium of which about 50% is sequestered in bone. The extracellular fluid contains between 1 and 5%, with the balance located in the intracellular compartment. Only about 1% of magnesium is present in the blood plasma and red cells.

Normal plasma concentrations of magnesium range from 0.70 to 1.05 mmol/L (Saris et al., 2000, Anderson, 2001, Beer et al., 2006).

Magnesium is a cofactor for more than 360 enzymatic reactions in the body involving energy metabolism including those related to adenosine triphosphate (ATP) metabolism, glucose utilisation, muscle contraction and synthesis of fat, protein, and nucleic acids. It is also involved in intermediary metabolic processes, neuromuscular activity, cardiovascular health and bone metabolism. (Fawcett et al., 1999, Newhouse et al., 2002).

A number of disease states are associated with hypomagnesaemia. These include cardiovascular diseases, neuromuscular disorders, renal diseases, drug toxicities, asthma, migraines, premenstrual syndrome, pre-eclampsia, eclampsia, osteopenia, atherosclerosis and hypertension (Resnick et al., 1994) (Newhouse et al., 2002). In particular conditions specifically related to glucose metabolism such as diabetes mellitus (Lopez-Ridaura et al., 2004), insulin resistance (Paolisso & Barbagello, 1997, Huerta et al., 2005) and obesity. (Guerrero-Romero & Rodr#305;quez-Moran, 2002) are also associated with hypomagnesaemia.

Plasma concentrations of magnesium are kept within a narrow range and although the exact physiological mechanisms which regulate this are not fully understood they are believed to be a function of dietary intake, renal and intestinal processes. Absorption of magnesium occurs primarily in the ileum and colon. This absorption is inversely related to dietary intake; ranging from about 65% at a low dietary intake to about 11% at high intakes. Factors controlling magnesium absorption are not entirely understood. Studies suggest a number of hormones play a role in affecting magnesium balance including parathyroid hormone (PTH) and calcitonin, vitamin D, insulin, glucagon, antidiuretic hormone, aldosterone and sex steroids hormones. (Muneyyirci-Delale et al., 1998, Saris et al., 2000). Good sources of magnesium include wholegrains, nuts, beans, legumes and green leafy vegetables. The Australian recommended daily intake of for adults ranges from 270 – 340mg/day (Braun & Cohen, 2005).

Magnesium Research

Londono and Rosenbloom (1971) were the first to demonstrate, in diabetic children, that a glucagon injection caused a significant decline in plasma concentration of magnesium. Subsequently, Rosenbloom (1977) observed that the decline in plasma magnesium detected during an oral glucose tolerance test was less in children and adolescents with pre-diabetes than in healthy control subjects. Rosenbloom concluded that that abnormalities in magnesium metabolism may occur very early in the course of the development of diabetes mellitus.

Magnesium is a cofactor of numerous enzymes involved in glucose metabolism and plays a significant important role in the action of insulin. In particular it has been shown that magnesium plays the role of a second messenger for insulin action and is a key mineral for both appropriate glucose utilisation and insulin signalling. Cellular magnesium deficiency is associated the impaired function of numerous enzymes which use high energy phosphate bonds, which are involved in glucose metabolism, and require magnesium as a cofactor. Low erythrocyte magnesium content increases membrane microviscosity and this mechanism may impair the interaction of insulin with its receptor on the plasma membrane (Paolisso et al., 1990).

Insulin itself has been demonstrated to be an important regulatory factor in the accumulation of intracellular magnesium. Concentrations of intracellular magnesium have been found to be low in those with type 2 diabetes. In individuals with type 2 diabetes an inverse association exists between plasma magnesium and insulin resistance. Insufficient intracellular magnesium may result in defective tyrosine kinase activity. Impaired tyrosine kinase activity impairs appropriate receptor function and insulin action by influencing the activity of receptors after binding or by

influencing intracellular signalling and processing resulting in decreased insulin sensitivity. Intracellular magnesium deficiency may influence the development of insulin resistance and alter cellular glucose uptake (Saris et al., 2000, Takaya et al., 2004).

The reasons why magnesium deficiency is commonly found in diabetics are not clear, but may include increased losses of urinary magnesium, lower absorption of magnesium and lower dietary intake or factors related to insulin resistance. Increased urinary losses due to glucosuria and osmotic diuresis are one of the causes of low magnesium status in diabetics. Individuals with type 2 diabetes are also frequently overweight or obese, and may consume a diet higher in fat and energy and lower in magnesium than non-diabetics (McNair et al., 1982, Fujii et al., 1982, Takaya et al., 2004).

Hypomagnesaemia is a common feature in individuals with type 2 diabetes and although diabetes can induce hypomagnesaemia, magnesium deficiency may be a risk factor for type 2 diabetes (Tosiello, 1996). Low levels of serum magnesium have been found in 25 – 39% of outpatient diabetics in the USA (Nadler, 1995). Similar findings have also been reported in several European countries such as Italy, Austria and Sweden (Paolisso et al., 1988, Sjogren et al., 1988, Schnack et al., 1992).

Several studies have found an association between serum magnesium levels or dietary intake and insulin resistance or the development of type 2 diabetes.

In the Atherosclerosis Risk in Communities (ARIC) study using a cross-sectional design, investigators examined the associations of serum and dietary magnesium with the prevalence of diabetes, fasting insulin, cardiovascular disease and hypertension. The study consisted of 15 248 male and female subjects, black and white, aged 45-64 years. Serum magnesium levels were significantly lower in subjects with diabetes, cardiovascular disease and hypertension than in those without these diseases. In those without cardiovascular disease, serum magnesium levels were also inversely associated with glucose, insulin levels and systolic blood pressure. Dietary magnesium intake was inversely associated with insulin levels, high density lipoprotein-cholesterol, systolic and diastolic blood pressure. Both serum magnesium levels and dietary magnesium intake were lower in blacks than in whites. (Ma et al. 1995).

A subsequent ARIC study assessing the risk of type 2 diabetes associated with low serum magnesium and low dietary magnesium intake in a cohort of 12 128 non-diabetic adults over a 6-year period found a graded inverse relationship between serum magnesium levels and development of type 2 diabetes in white participants. Among white participants, low serum magnesium level was found to be a strong, independent predictor of type 2 diabetes. A weak or no association was observed in black participants. This study did not find an association between dietary magnesium intake and the risk for incident type 2 diabetes in either black or white participants. This was the first study to establish an association between low serum magnesium level and incident diabetes prospectively in humans. The authors suggest that the finding that low dietary magnesium intake was not associated with risk for type 2 diabetes may imply that compartmentalisation and renal handling of magnesium is a factor in the relationship between low serum magnesium levels and type 2 diabetes risk. The authors do however also make the point that the validity and reliability of the dietary assessment of intake of magnesium in the study are unknown (Kao et al., 1999).

Lopez-Ridaura et al. (2004) examined the association between magnesium intake and risk of type 2 diabetes. In a large prospective cohort study researchers followed 85 060 women and 42 872 men with no history of diabetes at baseline. Magnesium intake was evaluated using a food frequency questionnaire every 2–4 years. After 18 years of follow-up in women and 12 years in men, findings indicated a significant inverse association between magnesium intake and risk of type 2 diabetes.

A diet high in wholegrains and other sources of magnesium helped reduce risk for type 2 diabetes

in US black women, according to the results of a prospective cohort study. Inverse associations between magnesium and risk of type 2 diabetes have reported in predominantly white populations. This study examined magnesium, calcium, and major food sources in relation to type 2 diabetes in African-American women. The study included 41 186 women enrolled in the Black Women's Health Study who had no history of diabetes at baseline. During 8 years of follow-up between 1995–2003, the investigators documented 1 964 newly diagnosed cases of type 2 diabetes. The findings indicate that a diet high in magnesium-rich foods, particularly wholegrains, is associated with a significantly lower risk of type 2 diabetes in US black women. Higher calcium intake was not independently associated with risk of type 2 diabetes. The authors suggest that the protective effects of magnesium against the development of type 2 diabetes is particularly relevant for US African-Americans, who tend to have lower mineral intakes than other US ethnic groups (van Dam et al., 2006).

Colditz et al. (1992) analyzed data from a prospective cohort of 84360 US women. During 6 years of follow-up 702 cases of type 2 diabetes were diagnosed. After controlling for body mass index, previous weight change, and alcohol intake investigators observed no associations between energy intake, protein, sucrose, carbohydrate, or fibre and risk of diabetes. Potassium, magnesium, and calcium were each significantly inversely related to risk of diabetes.

In a similar prospective cohort study investigators found, after adjustment for potential non-dietary confounding variables, a strong inverse association between wholegrain, total dietary fibre, cereal fibre, and dietary magnesium intakes with the incidence of type 2 diabetes. The strong inverse relationship between dietary magnesium intake and risk of type 2 diabetes remained after adjustment for cereal fibre and grain intake (Meyer et al. 2000).

A recent study assessing the association between dairy intake and insulin resistance found no association between dairy intake and insulin sensitivity. Associations were positive for magnesium and calcium intake after adjusting for demographic, non-dietary lifestyle and dietary factors, and food groups. Data was obtained from the Insulin Resistance Atherosclerosis Study (1992-1999) for 1 036 US adults. This study suggests that magnesium and calcium intake specifically, but not dairy intake, is associated with insulin sensitivity (Ma et al., 2006).

Even in normal non-diabetic subjects, plasma hypomagnesaemia is associated with relative insulin resistance, glucose intolerance, and hyperinsulinemia.

Nadler et al. (1993) investigated the impact of a low magnesium diet in a small study consisting of 16 normal subjects that were within 120% of ideal body weight. Investigators found that a low magnesium diet reduced both serum magnesium and intracellular free magnesium in red blood cells resulting in a decrease in insulin sensitivity. The authors suggest that magnesium deficiency could provide a link between insulin resistance and altered vascular function associated with hypertension.

Rosolova et al., (1997) studied the effects of a 75-g oral glucose load on eighteen non-diabetic volunteers. This study despite being a small study to was first the first human study, according to the researchers, to demonstrate a relationship between magnesium concentration and insulin-mediated glucose disposal in non-diabetic subjects. The study suggests that the association between hypomagnesaemia and insulin resistance is not limited to those with type 2 diabetes but may also apply to non-diabetic individuals. This results also demonstrated that the lower the magnesium concentration the greater the insulin resistance.

Similar results were obtained in a subsequent study in healthy non-diabetic women. In a cohort of middle-aged healthy women selected from the Nurses Health Study, Fung et al. (2003) examined the association between magnesium intake and fasting insulin levels. Following adjustment for variables recognised to correlate with insulin concentration such as age, body mass index, and other lifestyle factors, investigators found that magnesium intake was inversely associated with fasting insulin concentration. The inverse association remained when magnesium only from food

sources was considered.

Huerta et al., (2005) studied the association between magnesium deficiency and insulin resistance in 24 obese non-diabetic children. Serum magnesium was significantly lower in obese children compared with lean children and was inversely correlated with fasting insulin. Obese children were also more likely to be relatively insensitive to insulin or insulin resistant. Dietary magnesium intake was significantly lower in obese children and was inversely associated with fasting insulin.

Studies examining the effects of supplemental magnesium have also been conducted. De Lourdes Lima et al, (1998) examine the effect of magnesium supplementation on the metabolic control of type 2 diabetes. It was found that magnesium supplementation improved glycaemic control in the groups taking higher than normal levels of magnesium supplementation.

In a randomised double-blind controlled trial, subjects with type 2 diabetes and decreased serum magnesium received either magnesium or placebo daily for 16 weeks. At the end of the study, subjects who received magnesium supplementation had significantly higher serum magnesium concentrations, increased sensitivity to insulin, lower fasting glucose levels and lower HbA1c than control subjects Rodríguez-Morán & Guerrero-Romero, 2003).

In a three-month double-blind randomized placebo-controlled trial, Guerrero-Romero et al., (2004) assessed the effects of oral magnesium supplementation (2.5g of magnesium chloride 2.5g, equivalent to 300 mg of elemental magnesium/day) on insulin sensitivity in sixty non-diabetic subjects. Although not diabetic these subjects had decreased serum magnesium levels and insulin resistance. Findings demonstrated that magnesium supplementation improved insulin sensitivity in these hypomagnesaemic individuals.

In a meta-analysis, Song et al., (2005) assessed the effectiveness of oral magnesium supplementation on glycaemic control in type 2 diabetes. Nine double-blind randomised trials were identified. Magnesium was found to be effective in reducing plasma glucose levels.

Conclusions

Type 2 diabetes and insulin resistance is characterised by intracellular and extracellular magnesium depletion. Epidemiologic studies showed a high prevalence of hypomagnesaemia and lower intracellular magnesium concentrations in those with type 2 diabetes and poor sensitivity to insulin. Both insulin and glucose are significant regulators of magnesium metabolism. In turn intracellular magnesium plays a key role in regulating the action of insulin action, insulin-mediated-glucose uptake and the tone of the vascular system. Reduced intracellular magnesium levels result in a defective action of tyrosine-kinase, impaired insulin action, and declining insulin sensitivity. Magnesium deficiency has been proposed as a one of the possible contributors to insulin resistance. Low dietary magnesium intake is also associated with the development of type 2 diabetes. Benefits of magnesium supplementation on the metabolic profile in diabetic subjects have been found in most, but not all clinical studies. Findings have suggested that daily magnesium administration and restoring appropriate intracellular levels, contributes to improved insulin-mediated glucose uptake. Despite the positive findings there is still a lack of consensus in the literature. Results of magnesium supplementation on glucose metabolism in established type 2 diabetes have been inconsistent. It is also noted that many of the studies have been relatively small and have used various protocols and types of magnesium. In many cases it is not always possible to separate the benefits of dietary magnesium from the foods it is found in. Larger prospective studies are required. However the current evidence suggests a likelihood that magnesium has an important role to play in treatment and prevention of type 2 diabetes and insulin resistance both from dietary sources and as supplement.

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