

Review

# Preventing Diabetes—What Is the Potential of Daily Water Intake and Its Mineral Nutrients?

Johannes Naumann<sup>1,\*</sup>, Diana Biehler<sup>1</sup>, Tania Lüty<sup>1</sup> and Catharina Sadaghiani<sup>1</sup>

<sup>1</sup> Interdisciplinary Center for Treatment and Research in Balneology, Institute for Infection Prevention and Hospital Epidemiology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg 79106, Germany

\* Correspondence: johannes.naumann@uniklinik-freiburg.de; Tel.: +49-761-270-82430

**Abstract:** To address the question whether there is evidence that drinking water in general or mineral water in particular is effective in preventing diabetes; we performed a literature search of randomized controlled trials (PubMed). The search resulted in very few trials (N = 9) investigating this topic: one trial investigates the effect of increasing water consumption on glycemic control in diabetic patients; two trials investigate the effect of drinking water with a meal in diabetic patients; while six trials compare the effect of mineral rich water with that of low mineralized water on glucose metabolism in healthy subjects. There is evidence that increasing water consumption can improve glucose metabolism and randomized controlled trials with mineral water suggest that waters containing relevant amounts of magnesium can exert an additional effect. The role of bicarbonate; which is present in all the mineral waters used in the trials; will be discussed. Future research needs to investigate the effect of mineral water in prediabetic individuals or individuals with impaired glycemic control.

**Keywords:** diabetes; water intake; mineral water; magnesium; bicarbonate; review; prevention

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## 1. Introduction

The incidence of type 2 diabetes mellitus, pre-diabetes, impaired glucose tolerance and metabolic syndrome has increased considerably worldwide. The global prevalence of diabetes is estimated to be 8.8 %, i.e. there are 415 million diabetics worldwide and 59.8 million diabetics in Europe (9.1 %) alone. In Germany, 7.2 % of males and 7.5 % of females are affected by diabetes. Adding a further 2.1 % for undetected cases, approximately 9.3 % of the German population is affected [1]. In 2008, diabetes led to direct costs, i.e. costs for medication and medical fees, of 6.3 million Euros in Germany, with additional costs for non-productive time and invalidity pensions [2].

Making lifestyle changes is the most effective way to reduce the risk of developing diabetes by an estimated 34 – 43 % [3]. Life style changes include a healthy diet and sufficient physical activity of 150 min a week, which should result in a weight loss of 7 %.

A healthy diet includes healthy drinking, because sugar sweetened beverages may add to excessive calorie intake, heightening the risk of obesity and associated diseases [4]. Increasing water consumption right before or during a meal curbs the appetite and reduces calorie intake [5].

Moreover, mineral nutrients such as bicarbonate and magnesium, in particular, are thought to affect glucose metabolism. An increased dietary acid load is associated with the development of insulin resistance [6] while a pre-existing diabetes favours acidosis, which, in turn, leads to increased insulin resistance [7].

This review explores to what extent drinking tap water or mineral water influences the risk for diabetes and impaired glucose tolerance. The results of the randomized controlled trials (RCTs) found through the literature search will be discussed alongside pathophysiological aspects as well as results from interventional studies using mineral nutrient supplements and animal trials.

## 2. Methods

To evaluate the influence of water intake on glucose metabolism, we performed a systematic literature search from March 30<sup>th</sup>, 2017 for RCTs in the PubMed database using the following terms:

(Diabetes OR impaired glucose tolerance OR insulin resistance) AND (Drinking water OR mineral water) AND (Randomized controlled trial OR Review OR Crossover).

RCTs and cross-over trials were included, if a parameter for glucose control was investigated (Figure 1). Only trials in English, German, Spanish and French were included.

### Measurement parameters (with normal values) for glycemic control

**Fasting glucose (< 110 mg/dl)**

**Glucose level 2 h after glucose loading (< 140 mg/dl)**

**Fasting insulin (6 - 25 mU/l)**

**Insulin after glucose loading (< 200 mU/l)**

**HOMA-IR (< 2)**

Product of fasting insulin [ $\mu$ U/ml]  $\times$  fasting glucose [mg/dl] / 405

Measure for insulin resistance

**Glycated hemoglobin, HbA1c (< 6 %)**

Percentage of glycated hemoglobin

Measure for blood glucose levels during the last 1 to 3 month

**Glycoalbumin (11 % - 16 %)**

Percentage of glycosylated blood proteins

Measure for blood glucose levels in the last 2 to 4 weeks

**Fructosamin (200 – 290  $\mu$ mol/l)**

Result from glycation reactions between a sugar and a primary amine.

Measure for blood glucose levels in the last 1 to 3 weeks

**Figure 1.** Measurement parameters for glycemic control

## 3. Results

Our systematic literature search yielded 168 trials, 156 of which were excluded by two independent reviewers based on their titles, thus leaving twelve trials.

After reading the abstracts another seven trials were excluded:

- three were not RCTs or cross – over trials ([8], [9], [10])
- one trial compared alcoholic beverages and water [11]
- three reviews investigated the correlation between water intake and its influence on body weight and health, but failed to cite RCTs on risk of diabetes or impaired glucose tolerance ([12], [13], [5]).

Therefore, three RCTs and two cross – over trials were left for review ([14], [15], [16], [17], [18]).

After reviewing references four additional RCTs ([19], [20], [21], [22]) were included. Hence, nine trials were reviewed. Our search did not reveal a systematic review of RCTs dealing with our research objective. Of the trials screened, one examined the effect of increased water intake [18], two trials examined the immediate effect of drinking water with a meal ([14], [15]) (Table 1), six trials compared the effect of low mineralized water (tap water) with the effect of mineral rich water ([16],[17],[19],[20],[21],[22]) (Table 2, 3). All investigated mineral rich waters were bicarbonate rich waters.

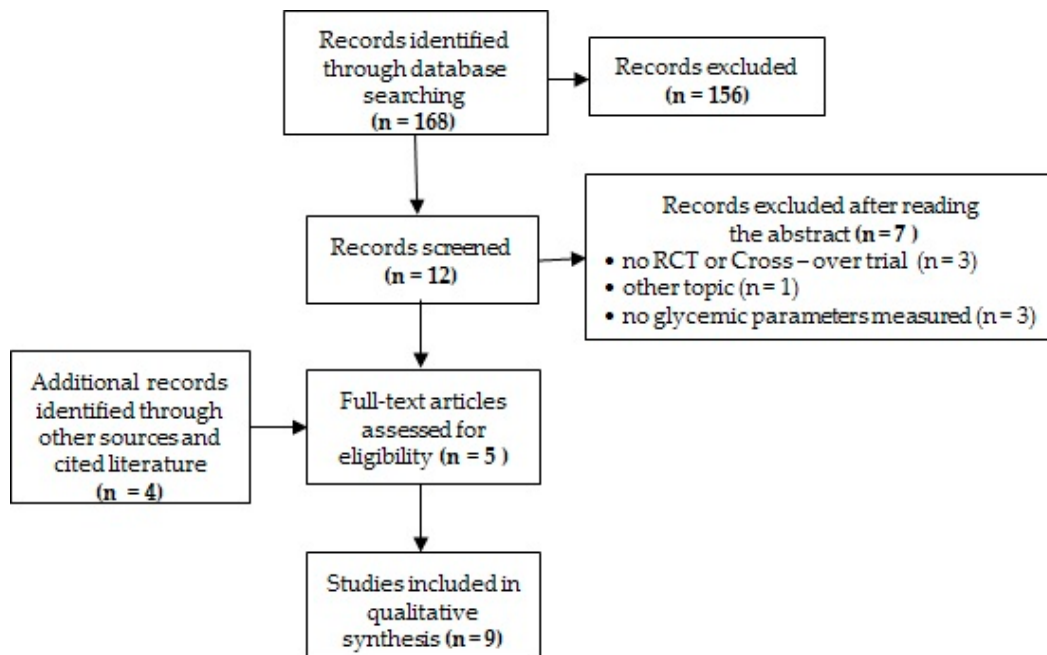


Figure 2. Flow-chart of the literature search

Table 1. RCTs with tap water as intervention

Study	Intervention	Participants	Parameters	Results
<sup>2</sup> Madjd et al., 2017 [18]	Single blind randomized study Women participating in a weight loss program did or did not substitute one sugar sweetened beverage (SSB) per day with for 24 weeks.	81 overweight and obese women with type 2 diabetes between 18 and 50 years	Body weight, fasting insulin, insulin sensitivity, glucose tolerance	Women in both groups lost weight and improved their glycemic control. Women who substituted one SSB with water had significant weight loss lost more weight had a lower fasting insulin had better insulin sensitivity and were better in the glucose tolerance test compared to the control group after 24 weeks.
<sup>1</sup> Torsdottir et al., 1989 [14]	Crossover trial. After overnight fasting, participants were served a meal with or without 300 ml of water.	7 healthy adults and 20 patients with type 2 diabetes	Postprandial glucose and insulin response	In healthy and well-controlled diabetic patients peak blood glucose increased significantly. In healthy subjects serum insulin and overall blood glucose response also increased with addition of water. In poorly-controlled diabetic patients, however, the addition of water did not display significant effects.
<sup>1</sup> Gregerson et al., 1990 [15]	Crossover trial. Participants were served a meal with 90 ml or 600 ml of water, respectively. The meal with 90 ml was eaten in either 10 min or 30 min.	10 patients with type 2 diabetes	Postprandial glucose and insulin response	Neither the amount of water nor the duration of the meal had a significant effect on glycemic and insulinemic response.

<sup>1</sup> study investigating immediate effects; <sup>2</sup>studies investigating medium-term effects.

**Table 2.** Crossover trials comparing the effects of **bicarbonate rich mineral water** with tap water

Study	Intervention	Water composition	Participants	Parameters	Results
<sup>1</sup> Schoppen et al., 2007 [17]	3 – way randomized crossover study, where 3 waters were tested by drinking 0.5 l with a standardized meal. Glycemic parameters were measured up to 120 min postprandial.	Two bicarbonate rich mineral waters were tested: a) 2094 mg/l HCO <sub>3</sub> <sup>-</sup> + 1117 mg/l Na <sup>+</sup> + 583 mg/l Cl <sup>-</sup> + 5,7 mg/l Mg <sup>2+</sup> + 55 mg/l K <sup>+</sup> ; b) 2013 mg/l HCO <sub>3</sub> <sup>-</sup> + 948 mg/l Na <sup>+</sup> + 592 mg/l Cl <sup>-</sup> + 9,7 mg/l Mg <sup>2+</sup> + 48 mg/l K <sup>+</sup> Control water: 71.1 mg/l HCO <sub>3</sub> <sup>-</sup> + 9 mg/l Na <sup>+</sup> + 5.7 mg/l Cl <sup>-</sup> + 2.7 mg/l Mg <sup>2+</sup> + 1.4 mg/l K <sup>+</sup>	18 healthy postmenopausal women aged 51 to 59	Postprandial blood glucose - and insulin concentration	Drinking one of the two bicarbonate rich mineral waters resulted in significantly lower insulin concentrations at 120 min after the meal. No differences in glucose concentration were found.
<sup>2</sup> Toxqui et al., 2016 [16]	Randomized controlled single-blinded crossover trial. For 8 weeks 1 l of the test water was drunk? daily followed by an 8-week washout period before testing the control water Controlled crossover trial. For 8 weeks 1 l of the test water daily with an 8-week washout period before testing the control water	Bicarbonate rich test water: 2050 mg/l HCO <sub>3</sub> <sup>-</sup> + 1090 mg/l Na <sup>+</sup> + 622 mg/l Cl <sup>-</sup> + 5.8 mg/l Mg <sup>2+</sup> Control water: 75 mg/l HCO <sub>3</sub> <sup>-</sup> + 7.6 mg/l Na <sup>+</sup> + 4.8 mg/l Cl <sup>-</sup> + 2.8 mg/l Mg <sup>2+</sup>	72 healthy adults aged 18 to 45, with moderately elevated cholesterol levels	Fasting glucose and fasting insulin	Drinking both waters resulted in a significant reduction of fasting glucose and LDL – cholesterol.
<sup>2</sup> Pérez-Granados et al., 2010 [21]	Controlled crossover trial. For 8 weeks 1 l of the test water daily with an 8-week washout period before testing the control water	Bicarbonate rich test water: 2120 mg/l HCO <sub>3</sub> <sup>-</sup> + 1102 mg/l Na <sup>+</sup> + 597 mg/l Cl <sup>-</sup> + 9.4 mg/l Mg <sup>2+</sup> control water: 104 mg/l HCO <sub>3</sub> <sup>-</sup> + 8.7 mg/l Na <sup>+</sup> + 11 mg/l Cl <sup>-</sup> + 5.0 mg/l Mg <sup>2+</sup>	18 healthy adults aged 18 to 40, with moderately elevated cholesterol levels	Fasting glucose and fasting insulin	Compared to control water fasting glucose decreased with the bicarbonate rich water but not significantly (p = 0.056).
<sup>2</sup> Schorr, 1996 [22]	Randomized, placebo-controlled, double blind crossover trial. For 4 weeks 1.5 l of the test water with a 2-week washout period before testing the control water	Bicarbonate rich test waters: a) 879 mg/l HCO <sub>3</sub> <sup>-</sup> + 1295 mg/l Na <sup>+</sup> + 1507 mg/l Cl <sup>-</sup> + 9.7 mg/l Mg <sup>2+</sup> b) 1983 mg/l HCO <sub>3</sub> <sup>-</sup> + 602 mg/l Na <sup>+</sup> + 152 mg/l Cl <sup>-</sup> + 53 mg/l Mg <sup>2+</sup> control water: < 0.2 mmol/l HCO <sub>3</sub> <sup>-</sup> + < 0.1 mmol/l Na <sup>+</sup> + < 0.1 mmol/l Cl <sup>-</sup> + < 0.1 mmol/l Mg <sup>2+</sup>	21 healthy adults between 60 and 72 years	Plasma glucose, plasma insulin and glucose tolerance	No significant effect was found.

<sup>1</sup> study investigating immediate effects; <sup>2</sup>studies investigating medium-term effects.

**Table 3.** Controlled trials comparing the effects of **bicarbonate and magnesium rich mineral water** with tap water

Study	Intervention	Water composition	Participants	Parameters	Results
Gutenbrunner, 1993 [19]	Randomized, controlled, single blind trial. For 28 days, participants drank 1.4 l daily of a bicarbonate and magnesium rich water or control water.	Bicarbonate and magnesium rich water: 2946 mg/l HCO <sub>3</sub> <sup>-</sup> + 967 mg/l Na <sup>+</sup> + 128 mg/l Cl <sup>-</sup> + 102 mg/l Mg <sup>2+</sup> control water: 150 mg/l HCO <sub>3</sub> <sup>-</sup> + 19.8 mg/l Na <sup>+</sup> (magnesium concentration is not mentioned)	24 healthy men between 19 and 31 years	Fasting glucose fasting insulin glucose tolerance serum fructosamin	Men drinking the bicarbonate and magnesium rich water had significantly lower serum concentrations of fructosamin and glucose concentrations 30 min after glucose loading compared to men drinking control water.
Murakami et al., 2015 [20]	Controlled crossover trial. Participants drank 0,5 l of each water for one week in two cycles. The intervention lasted 4 weeks: CW/BMW/CW/BMW	Bicarbonate and magnesium rich water (BMW) : 2485 mg/l HCO <sub>3</sub> <sup>-</sup> + 412 mg/l Na <sup>+</sup> + 182 mg/l Cl <sup>-</sup> + 291 mg/l Mg <sup>2+</sup> control water (CW): 28 mg/l HCO <sub>3</sub> <sup>-</sup> + 10 mg/l Na <sup>+</sup> + 11 mg/l Cl <sup>-</sup> + 1.9 mg/l Mg <sup>2+</sup>	19 healthy adults between 26 and 59 years	Fasting plasma glucose serum glucose insulin glycoalbumin	After the periods of drinking bicarbonate and magnesium rich water, glycoalbumin concentrations were significantly lower. No differences were found for glucose and insulin concentrations.

## 4. Discussion

### 4.1. Effect of water intake

#### 4.1.1 Effect of increased water intake

The effect of water intake on glucose metabolism and body weight was investigated in a single-blinded randomized trial in 62 obese women, who participated in a weight loss program for 24 week [18] (Table 1). One half of the participating women replaced diet drinks with water. Women in both groups lost weight and improved their glucose metabolism. However, the effect in the group of women substituting diet drinks with water was significantly higher. The substitution group had more substantial weight loss, a lower insulin concentration, lower insulin resistance and lower glucose concentration 2 h after food intake. Hence, substitution of diet drinks with water showed a positive influence on glucose metabolism.

Two observational studies examined the relationship between water intake and hyperglycaemia (defined as an elevated blood sugar level) or diabetes risk, respectively. During a nine-year follow-up 565 of 3,615 participants developed hyperglycaemia, whereas 202 of 3,615 participants (male & female) developed diabetes [23]. The risk of hyperglycaemia was significantly lower (20 – 30 %) in participants drinking more than 0.5 l of water daily compared with drinking less. In this study, as well as in the following, the increase in water intake was significantly correlated with decreased intake of sugary and alcoholic beverages. Comprising a 13-year follow up, the second study was not able to show a significant correlation between water intake and diabetes risk. Yet, the authors calculated that daily substitution of one sugar-sweetened drink for water decreases the diabetes risk by 7 % [24].

One cross-sectional study calculated a type 2 diabetes risk score for 138 healthy adults taking into account age, gender, BMI, waist circumference, ethnicity and family history regarding diabetes and blood pressure and correlated it with the participant's daily water intake. An increase of 240 ml in water intake revealed a significant decline in the type 2 diabetes risk score [9]. All of the four groups formed based on their diabetes risk score had a daily fluid intake of 2.5 l. The ratio of water intake to liquid intake increased with a lower diabetes risk score.

A nutrition survey examined the relationship between the quantity of water taken in and HbA1c in 1,035 participants. In male participants with HbA1c < 5.5 %, the proportion of water to total liquid intake was significantly higher (17 % and 10 % respectively) than in males with HbA1c > 5.5 %. Based on this finding, the authors calculated that an increase of 240 ml in daily water intake reduces the risk of elevated HbA1c > 5.5 % by 22 % in men but not in women [25].

In summary, this indicates that sufficient water intake reduces diabetes risk. This may be due to concomitant dietary habits. An observational study in the USA comprising 18,311 participants showed that a higher water intake was accompanied by a decrease in total intake of calories, sugary beverages, total fat, saturated fats, sugar, sodium and cholesterol [26]. This effect was greater in males under the age of 65.

Conversely, a survey of 75 countries showed that a 1% rise in soft drink consumption was associated with an additional 0.3 adults per 100 adults developing diabetes [27].

#### 4.1.2. Effect of drinking water with a meal

Two RCTs investigated the postprandial glycemic effect of drinking water with a meal (Table 1). One study with non-insulin dependent diabetic patients compared the effect of drinking 90 ml of tap water and 600 ml of tap water with a meal on postprandial glucose and insulin [15]. Neither the volume of ingested water nor the consumption time of the meal (10 vs. 30 min) showed an effect.

The other RCT compared the postprandial glycemic response after a meal taken with or without 300 ml of tap water [14]. In seven healthy and twelve well-controlled diabetic patients, peak blood glucose increased significantly. In healthy subjects serum insulin and overall blood glucose response also increased with the addition of water. Conversely, in poorly-controlled diabetic patients, the addition of water did not yield significant effects.

The effect is possibly attributed to acceleration of the gastric emptying rate of carbohydrates with the addition of even as little as 90 ml of water,

#### 4.2. Effect of mineral rich water

All trials comparing the effect of tap water and mineral water used bicarbonate-rich mineral water, since a high dietary acid load is associated with increased insulin resistance as well as with disturbed glucose metabolism. The following section highlights some studies investigating the effect of bicarbonate on glucose control.

A recent intervention study [28] in diabetic patients with chronic kidney disease showed that compared with a placebo, supplementation with bicarbonate targeting a serum concentration of 24 – 28 mmol/l significantly improved multiple parameters of glucose metabolism. For example, the serum glucose concentration decreased from 127 mg/dl to 110 mg/dl, the proportion of glycated haemoglobin declined from 7.7 to 6.7 %, insulin resistance (HOMA-IR) decreased from 6.1 to 7.0, and serum insulin concentration decreased from 13.4 mIU to 19.9 mIU. Insulin resistance declined up to a bicarbonate concentration of 28 mmol/l, however, it increased when 28 mmol/l of bicarbonate was exceeded. . Thus, the improvement in insulin resistance was based on a correction of acidosis rather than on the serum bicarbonate concentration itself. Mild acidosis is accompanied by increased insulin resistance even in healthy subjects.

A cross-sectional study [29] investigated the relationship between serum hydrogen carbonate concentration and insulin resistance in 1,496 healthy adults. Participants with lower serum hydrogen bicarbonate concentration showed both significantly increased insulin resistance and a significantly elevated serum insulin concentration. This effect was even more distinct in participants with higher BMI. Similarly, a recent study [6] revealed a relationship between an increased lactate concentration, which is an indicator for mild metabolic acidosis, and insulin resistance in 104 sedentary adults.

The relevance of serum hydrogen carbonate in prevention was reported in a prospective study in 630 women ( $\bar{O}$  = 56 years) and a 10-year follow up. Women with lower serum hydrogen carbonate concentrations had a significant higher risk of developing type 2 diabetes than women with higher serum hydrogen carbonate concentrations [30].

##### 4.2.1. Effect of bicarbonate-rich water

The studies investigating the effect of mineral-rich water on glucose metabolism were conducted in healthy individuals (Table 2). Two studies focused on fat metabolism examined participants with moderately increased cholesterol levels ([16],[21]). All six studies in this section used mineral water rich in bicarbonate, two of which contained additional substantial magnesium concentrations ([19], [20]). One of these studies dealt with temporary effects [17] whereas the other five studies investigated the effects after several days or weeks ([16],[19],[20],[21],[22]).

Five studies ([16],[19],[20],[21],[22]) examined fasting blood glucose and fasting insulin levels. One of these studies additionally reported serum fructosamin concentrations and conducted glucose tolerance tests [19], while another study also measured the plasma glycoalbumin concentration [20].

An RCT investigated the temporary effect of drinking 0.5 l of two bicarbonate-rich mineral waters as compared to drinking water low in minerals [17]. Eighteen healthy, postmenopausal women consumed a standard meal accompanied by 0.5 l of one of the three waters. Two hours after the meal, no significant differences in glucose concentrations were observed between the groups. Only one of the two bicarbonated mineral waters induced a significantly lower insulin concentration 120 min after the meal and a significantly higher insulin peak after 30 min. However, this effect was only observed in four women with the lowest insulin sensitivity.

An RCT with cross-over design in 64 participants compared the intake of bicarbonate-rich mineral water with a mineral water low in minerals [16]. Drinking of both waters resulted in a significant decrease of the glucose concentration, total cholesterol and LDL-cholesterol. This effect was mainly attributed to an increased water intake (1 l/day for 8 weeks, two 8-week intervention phases with an 8 week wash-out phase in between) associated with a reduced calorie intake from beverages, especially sugary beverages. Nevertheless, reduction of the glucose concentration after



drinking the bicarbonated mineral water was more distinct (control water: Baseline: 4.9 mmol /l; after water drinking: 4.88 mmol /l and bicarbonated water: Baseline: 4.95 mmol/l; after water drinking: 4.8 mmol/l). A decrease in glucose concentration was not observed for either of the two waters.

Another RCT with a similar design in 18 participants compared the effect on fat and glucose metabolism of a bicarbonated water (2120 mg/l  $\text{HCO}_3^-$  + 9.4 mg/l  $\text{Mg}^{2+}$ ) with a water low in minerals (104 mg/l  $\text{HCO}_3^-$  + 5.0 mg/l  $\text{Mg}^{2+}$ ) [21]. Significant differences were not observed between the two waters. However, fasting blood glucose was lower after drinking bicarbonated water than after drinking water low in minerals ( $p = 0.056$ ). Besides, drinking both waters induced a reduction of the insulin concentration (Baseline:  $8.8 \pm 4.1$  mU/l, low mineral water:  $8.2 \pm 2.6$  mU/l, bicarbonate water:  $7.7 \pm 4.3$  mU/l).

Likewise, in another RCT [22] comparing the possible influence of a water low in minerals with both a water high in sodium bicarbonate and a water high in sodium chloride on blood pressure in healthy subjects eating a diet low in sodium there were no differences in either insulin nor glucose concentration.

These studies do not show a significant difference between the influence of water rich in minerals and water low in minerals on glucose and insulin concentration.

#### 4.2.2. Effect of bicarbonate and magnesium rich water

The following two studies tested mineral water containing not only bicarbonate but also substantial magnesium concentrations ( $> 100$  mg/l). They also determined the long-term blood sugar concentration (fructosamine or glycoalbumin concentration). One study additionally conducted a glucose tolerance test (Table 3).

In 1993, Gutenbrunner et al. [19] conducted a 4-week randomized and blinded mineral water cure in 24 healthy males. Participants received 1.4 l daily of either a water rich in hydrogen carbonate (2946 mg/l  $\text{HCO}_3^-$  + 102 mg/l  $\text{Mg}^{2+}$ ) or tap water (150 mg/l  $\text{HCO}_3^-$ , N/A  $\text{Mg}^{2+}$ ). Compared with tap water, after a glucose tolerance test, blood glucose concentrations declined significantly in the group receiving the water with hydrogen carbonate. This effect was still seen two days after the mineral water cure. Even the serum fructosamine concentration only declined in participants drinking mineral water high in hydrogen carbonate.

In a recent RCT [20] 19 healthy participants received 500 ml of bicarbonate-rich mineral water (2485 mg/l  $\text{HCO}_3^-$  + 291 mg/l  $\text{Mg}^{2+}$ ) for one week. The intervention period lasted one week, followed by a wash-out period with 500 ml tap water (28 mg/l  $\text{HCO}_3^-$  + 1.9 mg/l  $\text{Mg}^{2+}$ ) daily. Both procedures were repeated once. Similarly to previously mentioned studies, there were no significant differences in glucose concentration or insulin concentrations after drinking either of the waters. However, the concentrations tended to be lower after drinking the bicarbonate-rich mineral water. Indeed, after drinking the bicarbonate-rich water glycoalbumin concentrations decreased significantly.

Again, this study showed a significant decrease in the glycoalbumin concentration even after the first week of intervention with tap water compared to baseline, indicating that water intake alone had an effect. Additionally, the bicarbonate rich water had a significant effect.

Significant effects were only seen in trials measuring long-term blood glucose levels. This indicates that individual measurements in healthy participants do not differ significantly, but slight differences add up over time to measurable differences. In patients suffering from pre-diabetes, diabetes or metabolic syndrome one would expect a positive influence on the glucose and insulin concentrations. Yet, not a single study investigated the influence of mineral water on glucose metabolism in a group of afflicted/diseased subjects.

However, rats suffering from metabolic syndrome induced by fructose administration were used to compare the effect of drinking mineral-rich and bicarbonate-rich water to water with low mineral content.

#### 4.2.3. Effect of mineral rich water in an animal model

It is known that rats receiving 10 % fructose in their drinking water develop symptoms of metabolic syndrome and that the plasma glucose level increases considerably.

If fructose is administered in mineral water rather than tap water, the basic parameters of glucose metabolism e.g. glucose, insulin and triglyceride concentrations do not deteriorate at all or at least less [31]. Similarly, rats receiving fructose in tap water showed a strong increase in aldosterone level, whereas rats receiving fructose in mineral water had the same level as the control rats that did not receive any fructose. A review from 2016 [32] describes the relationship between elevated aldosterone level and both metabolic syndrome and type 2 diabetes.

Sirt1 and PGC1- $\alpha$  are proteins that counteract metabolic syndrome and aberrant glucose metabolism. Sirt1 positively influences multiple steps in glucose metabolism in the liver, the pancreas, muscles, and adipose tissue. De-acetylated PGC1- $\alpha$  is the main regulator of the sirt1 pathway [33], [34]. The expression of both proteins was significantly higher in liver tissue of rats receiving mineral water compared to rats receiving tap water [35]. Besides, the amount of phosphorylated insulin receptor substrate (IRS), the active form of the substrate that forwards the insulin signal, was elevated in liver tissues of rats receiving mineral water compared with rats receiving tap water [36]. This indicates increased insulin sensitivity. Though, both groups of rats taking in fructose had a lower level of phosphorylated IRS compared with control rats. This might be due to the fact that the serum magnesium concentration in rats receiving fructose significantly declined (1.71 mmol/l and 1.55 mmol/l respectively) [31].

Magnesium ions are essential for the auto-phosphorylation of the insulin receptor, as two magnesium ions bind the tyrosine kinase domain. Disruption of phosphorylation is considered the main mechanism leading to insulin resistance through lack of magnesium ions [37].

In summary, these animal experiments suggest that intake of mineral water in patients with either metabolic syndrome, pre-diabetes, or type 2 diabetes might have a positive influence.

Besides bicarbonate, magnesium seems to be important. Both RCTs studying effects of mineral water rich in magnesium determined long-term blood glucose concentrations. Hence, the positive effect observed in these studies cannot be traced back exclusively to magnesium. Still, the currently available data indicate a positive influence of magnesium on the glucose metabolism and one might assume that magnesium absorbed from mineral waters also positively influences glucose metabolism.

#### 4.3. Clinical trials considering magnesium

Results from studies investigating mineral waters containing relevant concentrations of magnesium are consistent with the results from studies investigating magnesium supplementation or intake of dietary magnesium. The latter demonstrated that in subjects suffering from magnesium deficiency, pre-diabetes, or insulin resistance, additional magnesium intake may ameliorate their glucose metabolism. Indeed, in 51 % of the subjects suffering from magnesium deficiency and pre-diabetes, magnesium supplementation of 382 mg/day positively influenced glucose metabolism compared to 7 % of the subjects in a placebo group [38]. In adults with low insulin sensitivity magnesium supplementation of 365 mg/day caused the serum glucose level to drop significantly and increased insulin sensitivity [39].

The most recent systematic review from 2016 including a meta-analysis of 21 randomized studies in 1,362 participants (684 individuals in Mg<sup>2+</sup> group and 678 individuals in control group) compared the influence of magnesium supplementation on insulin sensitivity and glucose metabolism in diabetic individuals with the influence in non-diabetic individuals [40]. This review demonstrated significant amelioration of insulin resistance in both diabetic and non-diabetic individuals. A significant reduction of the serum glucose concentration was observed in a subset of studies including only those with supplementation for at least four months and only considering participants with magnesium deficiency.

##### 4.3.1. Magnesium blood concentration

In 2012 [41], a case control study in 200 obese individuals revealed that the 50 diabetics had a lower serum magnesium concentration than the 150 participating non-diabetics. Forty-eight per cent of the diabetics had magnesium deficiency compared with only 15 % of the non-diabetics. Furthermore, a lower magnesium concentration was associated with a higher plasma glucose level, higher insulin resistance and a higher HbA<sub>1c</sub> concentration.

A prospective study explored this relationship in 8,555 participants with a follow-up period of 5.7 years [42]. A reduction in the serum magnesium concentration of 0.1 mmol was associated with an 18 % higher risk of developing diabetes (HR = 1.18; 95 % CI = 1.04 – 1.33) and a 12 % higher risk for pre-diabetes (HR = 1.12; 95 % CI = 1.01 – 1.25). In participants deficient in magnesium, the diabetes risk increased by 79 % (HR = 1.79; 95 % CI = 1.16 – 2.77) and the pre-diabetes risk increased by 44 % (HR = 1.44; 95 % CI = 0.91 – 2.27), however, the latter finding was not significant.

#### 4.3.2. Dietary magnesium

In 2011, a review with meta-analysis of 13 prospective studies in a total of 536,318 participants and 24,516 diabetes cases [43] showed a significantly reduced risk for type 2 diabetes: Increasing the daily magnesium intake by 100 mg was accompanied by a decrease in diabetes risk by 14 %.

The most recent meta-analysis (Fang et al., 2016) of 25 prospective studies comprising 637,922 participants revealed the following dose – effect – correlation: An increase of daily magnesium intake by 100 mg was associated with an 8 – 13 % lower diabetes risk [44].

Another meta-analysis including 6 cross-sectional studies in a total of 24,473 participants investigated the correlation between magnesium intake and metabolic syndrome [45]. This study revealed that daily intake of 100 mg magnesium was associated with a risk reduction by 17 %.

#### 4.3.3. Relevance of magnesium for glucose metabolism

A review by Gommers et al., 2016 [37] summarizes the multiple functions of magnesium on a molecular level. Another narrative review by Mooren, 2015 [46] sums up the molecular mechanisms and links them to data from clinical trials.

The binding of insulin to its receptor triggers a signalling cascade leading to import of glucose into the cell (muscle), to glycogen synthesis (liver) and lipid synthesis (adipose tissue). If this signalling cascade is impaired, more insulin is released into the bloodstream. When the increased amount of insulin is in the end also unable to trigger the signalling cascade sufficiently, blood sugar levels eventually rise.

Magnesium plays a direct role in the signalling cascade as a co-factor of the insulin receptor. Magnesium binds to the intracellular domain of the insulin receptor thereby allowing or enhancing transmission of the insulin signal induced by the extracellular binding of insulin to the receptor. Hence, magnesium increases insulin sensitivity.

It is known from studies in mice, that oral magnesium supplementation increases the number of glucose transporters in the cell membrane of muscle cells; , glucose can therefore be imported faster and more effectively [47].

An inflammatory environment also contributes to development of insulin resistance and is one of the main reasons for an obesity-related elevated diabetes risk. Thus, magnesium as an anti-inflammatory ion can counteract insulin resistance [48].

To prevent diabetes it is essential to preserve the function of  $\beta$ -cells [49]. A prospective study comprising 228 patients with disturbed glucose tolerance showed that the diabetes risk was smallest in participants with functioning  $\beta$ -cells at the beginning of the study [50]. The function of the  $\beta$ -cells was the strongest predictor for diabetes. In diabetic and non-diabetic participants, magnesium administration in the form of MgCl<sub>2</sub> increased the function of  $\beta$ -cells [51].

Insulin also influences kidney cells to increase re-absorption of magnesium. After binding of insulin to its receptor, TRPM6 is recruited to the plasma membrane; consequently, magnesium re-absorption is enhanced [52]. Therefore, insulin resistance leads to increased magnesium excretion starting a vicious cycle.

Most of the glucose ingested from food is absorbed into muscles. Deteriorated insulin resistance inhibits absorption into the muscles, whereby the reason for deterioration may either be magnesium deficiency or acidosis, in which bicarbonate might be an issue.

## 5. Limitations

The main limitation of this review is the small number of RCTs investigating the impact of mineral water on glucose metabolism. Furthermore, the studies had small numbers of participants and were carried out in healthy subjects thereby limiting the evidence for treatment of type 2 diabetes.

Nevertheless, existing observational studies, studies with animal models and interventional studies of minerals present in mineral waters suggest a probable positive effect of drinking water and especially mineral water on glucose metabolism.

## 6. Conclusions

Water is an ideal calorie-free and sugar-free beverage, which seems suitable to contribute to the reduction of the growing prevalence of type 2 diabetes and its pre-stages, as already recommended by several institutions such as the ADA [3] and the WHO [53].

Besides, drinking mineral water rich in bicarbonate and magnesium is an ideal addition to magnesium from food.

Due to the complexity of nutrition and the fact that studies investigating diabetes and nutrition often omit beverages, there are insufficient data to prove an association between intake of water, particularly bicarbonate or magnesium-rich mineral water and reduction in risk for diabetes.

Based on the reviewed pathophysiological data from trials in humans and animals and the epidemiological data, it can be assumed that drinking water or mineral water rich in magnesium and bicarbonate ameliorates glucose metabolism and reduces the risk of developing diabetes. Especially drinking mineral water for a longer period of time may have a positive effect.

Although the data are still inconclusive, from our point of view, drinking water or mineral rich water should be recommended to prevent and treat type 2 diabetes because of the absence of adverse effects.

Due to the high prevalence, the associated suffering and the resulting health expenditures, it is imperative to conduct RCTs to clarify the role of mineral water in prevention and treatment of diabetes.

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