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CLINICAL NUTRITION RESEARCH

Low Salt Diet and Insulin Resistance

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It is well known that high sodium intake is closely associated with the risk of cardiovascular disease, but the effect of low sodium intake on insulin resistance is not clear. In this article, we summarize findings from previous studies focusing on the association between low sodium intake and insulin resistance. While many investigations on this topic have been conducted actively, their major findings are inconsistent, partly due to different study designs. Thus, additional randomized controlled trials with an adequate study period and reasonable levels of low sodium intake are needed.

Key Words: Low sodium, Low salt, Insulin resistance

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Introduction

The excessive sodium intake is known to be closely related to cardiovascular diseases [1-3]. The increased sodium intake increases the risk of developing hypertension, stroke, stomach cancer, and renal diseases, which in turn increases the social costs [4-6]. The World Health Organization (WHO) reviewed 15 randomized controlled studies (167,656 total subjects) and showed that the low sodium diets effectively lower average blood pressure and the incidence of stroke and heart diseases [1,2]. In Korea, lowering sodium intake from 4.7 grams to 3 grams would provide economic and social benefit by 12.6 trillion won [7]. Thus, lowering sodium intake is cost-effective as it lowers social costs by decreasing the incidence of hypertension, cardiovascular diseases, stroke, stomach cancer, and renal diseases.

The adequate recommended sodium intake varies among different countries. Usually, 5–8 g is recommended based on regional food culture. The United Kingdom is making efforts to lower its sodium intake to 3 grams by the year of 2025 [8]. The WHO also aims to achieve sodium intake of < 2 g/day (approximately 90 mmol), or < 5 g/day of salt. The Institute of Medicine of the National Academies, co-founded by the United States and Canada, in its Dietary Reference Intake recommends 1.5 g/day of sodium (3.8 g of salt) with a tolerable upper intake of 2.3 g/day [9]. Asian cultures including Korea have higher sodium intakes [10]. The Korea recommends 2 g/day of

sodium (5 g/day of salt) [11], while the Japan recommends 6 g/day of salt intake [12]. Meanwhile, O'Donnell et al. [13] reported that estimated sodium intake (on the basis of 24 hr urinary excretion) between 3 g/day and 6 g/day was associated with a lower risk of death and cardiovascular events compared with either higher or lower estimated level of sodium intake.

However, the effect of low sodium diet on hyperlipidemia and insulin resistance is disputable. To date, it has been reported that low sodium intake lowers blood pressure but increases blood renin, aldosterone, noradrenaline, adrenaline, cholesterol, and triglyceride levels [2]. On the other hand, a systematic review did not show a significance for the association between low sodium intake and sympathetic activity and lipid profile in [14]. There have been many attempts, but the effects of low sodium intake on insulin resistance seem far more complicated. Recently, Patel et al. [15] reported that there was no statistical significance between dietary sodium reduction and fasting plasma glucose in their meta-analysis. Besides, the effects of low sodium intake on insulin resistance was heterogenous. The current article summarizes the contents of previous studies which focused on the association between low sodium diet and insulin resistance.

Table 1. Summary of studies on insulin sensitivity and sodium intake

	Author	Design	Method	N	Low vs. High (Na (g)/day)	Duration	IR	Wash-out
RCT	Perry et al. [20]	Crossover	Clamp	15	< 1.84 g vs. 2.3 g	5 day	↑	≥ 1 week
	Townsend et al. [21]	Crossover	Clamp	20	0.46 g vs. 4.6 g	6 day	↑	4 week
	Fliser et al. [22]	Parallel	Clamp	8	0.46 g vs. 4.6 g	7/3 day	↑	-
	Iwaoka et al. [23]	Crossover	OGTT	15	0.4 g vs. 4 g	8 day	↑	-
	Petrie et al. [24]	Crossover	Clamp	9	0.92 g vs. 3.68 g	4 day	↑	-
	Gomi et al. [25]	Crossover	Clamp	12	0.69 g vs 2.3 g vs. 4.6 g	7 day	↑	-
	Grey et al. [26]	Crossover	CIGMA	34	< 1.84 g vs. 4.6 g	7 day	-	-
	Sharma et al. [27]	Crossover	Insulin supp. test	18	0.46 g vs. 5.52 g	7 day	-	-
	Foo et al. [28]	Crossover	Clamp	18	0.92 g vs. 5.52 g	6 day	-	≥ 1 week
	Facchini et al. [29]	Crossover	Insulin supp. test	19	0.575 g vs. 4.6 g	5 day	-	-
	Meland et al. [30]	Crossover	OGTT	16	Moderate salt vs. Moderate salt + 1.15 g	4 week	-	-
	Suzuki et al. [31]	Crossover	Clamp	20	1.15 g vs. 5.86 g	7 day	-	-
	Inoue et al. [32]	Crossover	OGTT	14	0.23 g vs. 8.05 g	7 day	-	-
	Sharma et al. [33]	Crossover	OGTT	23	0.46 g vs. 5.98 g	6 day	↓	-
	Ames et al. [34]	Crossover	OGTT	21	Urine Na 2.66 g + Na 8 g	4 week	↓	-
	Kuroda et al. [35]	Crossover	HOMA	53	1-3 g vs. 12-15 g NaCl	7 day	↓	-
	Jun and Lee [36]	Parallel	HOMA	85	2 g vs. 5 g	16 weeks	↓	-
Non RCT	Garg et al. [37]	Cohort	HOMA	152	Urine Na < 0.46 g vs. > 3.45 g	7 day	↑	-
	Raji et al. [38]	Comparative	HOMA	426	0.23 g vs. 4.6 g	7 day	↑	-
	Nakandakare et al. [39]	Observation	HOMA	115	3.68 g → 1.38 g	7 → 21 day	↑	-
	Melander et al. [40]	Observation	Clamp	28	0.23 g → 5.52 g	7 day	-	-
	Dengel et al. [41]	Observation	Clamp	8	3 g vs. 10 g	2 week	-	-
	Dziwura et al. [42]	Observation	HOMA	41	0.23-0.46 g 5.06-5.52 g	7 day	↓	-
	Lima et al. [43]	Observation	HOMA	17	1.61 g vs. 6.83 g	7 → 91 day	↓	-
	Donovan et al. [44]	Comparative	Clamp	8	0.23 g vs. 4.6 g	5 day	↓	-

IR: insulin resistance, RCT: randomized controlled trial, Clamp: euglycemic calmp test, HOMA: homeostasis model assessment, OGGT: oral glucose tolerance test, CIGMA: continuous infusion of glucose with model assessment, ↑: increased insulin resistance, ↓: decreased insulin resistance, -: no change of insulin resistance.

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Main body

We searched the electronic databases MEDLINE and EMBASE to identify eligible studies that examined the association between sodium intake and insulin resistance through June 2015. Currently, 25 studies (17 randomized controlled trials and 8 observational studies) focusing on the association between sodium intake and insulin resistance have been published (Table 1).

However, the results seem quite interesting. For instance, the studies which relate low sodium diets to increased insulin resistance reported that limited sodium intake reduces body water contents, which is compensated by increased epinephrine, renin, and angiotensin levels, all of which inhibit the action of insulin and increase insulin resistance [2]. On the contrary, studies which investigate the relationship between low sodium diet and decreased insulin resistance suggest three main mechanisms. First, the low sodium intake lowers blood leptin levels, which causes reduction in size of abdominal fat cells, resulting in decreased obesity and insulin resistance [16,17]. Second, the low sodium diet regulates the expression of glucose transporter type-4 (GLUT4), the insulin receptors in fat cells, resulting in decreased insulin resistance [18]. Third, the angiotensin II level changes with low sodium diet which affects the action of insulin [19].

Although, there is inconsistency in results regarding the association between low sodium intake and insulin resistance; the following limitations further make it difficult to explain the cause-and-effect relationship between sodium intake and insulin resistance. Firstly most studies on insulin resistance and sodium intake conducted simple statistical analyses based on data which were primarily collected to find the association between sodium intake and hypertension. Secondly, most clinical trials were conducted for less than a week [20-22,24-29,30-33,35,37-39, 42,44]. Insulin resistance and diabetes are chronic illnesses which are impacted mostly by long term dietary habits, therefore, the short intervention periods might be insufficient to reach significant results. Thirdly, 15 out

Table 2. Associations between low salt diet and insulin resistance according to sodium restriction and intervention period

Author	N	Low Na	IR	Author	N	Low Na	IR
Moderate sodium restriction 1-2 g/day				Extreme sodium restriction < 1 g/day			
Foo M [28]	18	1 g	-	Townsend RR [21]	20	0.46 g	↑
Suzuki M [31]	20	1 g	-	Fliser D [22]	14	0.46 g	↑
Jun DW and Lee SM [34]	85	2 g	↓	Iwaoka T [23]	15	0.78 g	↑
				Sharma AM [27]	18	0.46 g	-
				Facchini FS [29]	19	0.57 g	-
				Inoue J [32]	14	0.23 g	-
Intervention period > 4 weeks				Intervention period < 4 weeks			
Meland E [40]	16	4 week	-	Townsend RR [21]	20	6 day	↑
Ames RP [34]	21	4 week	↓	Fliser D [22]	14	7/3 day	↑
Ministry of food and drug safety [34]	85	16 week	↓	Iwaoka T [23]	15	8 day	↑
				Perry CG [20]	15	5 day	↑
				Gomi T [25]	12	7 day	↑
				Sharma AM [27]	18	7 day	-
				Facchini FS [29]	19	5 day	-
				Inoue J [32]	14	7 day	-
				Suzuki M [31]	20	7 day	-
				Grey A [26]	34	7 day	-
				Foo M [28]	18	6 day	-
				Kuroda S [35]	53	7 day	↓

IR: insulin resistance, ↑: increased insulin resistance, ↓: decreased insulin resistance, -: no change of insulin resistance.

of 17 randomized controlled studies were cross-over studies. An important aspect of cross-over study is the wash-out period between the first and second intervention, which must be sufficient. However, as mentioned above, since the primary end point of most studies was to find an association between sodium intake and hypertension, in the designing these studies, the adequate wash-out periods might not be taken into account. Fourthly, several clinical trials [21-25,27-29,32,33,37,38,40,42,44] incorporated extremely low levels of sodium intake in the experiment and most of them limited sodium intake less than 0.5 g a day. Considering the fact that sodium intake should be close to the generally recommended 1 g for producing useful clinical change, therefore, the interpretation of data collected in studies using extreme sodium limitations must be cautious and demands further discussion. Fifthly, there was a lack of the information of genetic variations between individuals. Most studies did not consider their subject's 'sensitivity' to salt due to genetic variations in group assignment. The response to salt varies greatly between individuals, and this salt sensitivity results in differences in baseline values of factors such as insulin resistance. However most studies did not mention about such differences. Moreover, none of these studies consider the effect of pre-existing conditions of subjects such as hypertension and diabetes. Lastly, total energy consumption was different in control and intervention groups. None of studies focused on equality of caloric intake among control and intervention groups, and only a few studies incorporated controlled environments such as hospitalization during the experiment.

The main reasons explaining inconsistent findings of the studies might have been related to different definitions for 'low sodium intake' and variations in research durations. Thus, such studies must be interpreted with caution.

Based on the amount of sodium intake, the insulin resistance increased with extremely low sodium diets (less than 40 mmol/day of sodium (≒ 0.92 g/day of sodium, 2.34 g/day of NaCl), while no association was reported between insulin resistance and adequate sodium intake (Table 2).

Based on intervention periods, restricting sodium intake for more than 4 weeks resulted in decreased insulin resistance or no significant difference compared with control groups (Table 2). Studies with a short term showed that abrupt and short-term sodium restriction might stimulate sympathetic nervous system to increase blood catecholamine concentrations, which in turn increase the insulin resistance. However, four different studies carefully analyzed blood adrenalin levels (168 subjects) and showed that low-sodium diets did not influence blood adrenalin levels (6.90 pg/mL, 95% confidence interval (CIs): 2.17-15.96). Moreover, a meta-analysis of blood norepinephrine and low-sodium diets that included 7 studies (265 subjects) showed that the low-sodium diets did not affect blood noradrenalin levels (8.23 pg/mL, 95% CI: 27.84-44.29) [2].

As the sensitivity to salt intake varies among individuals and if this has been taken into account in a subgroup analysis the results might have shown that baseline sensitivity to insulin increases in salt- sensitive of subjects [27,33,35]. Although the

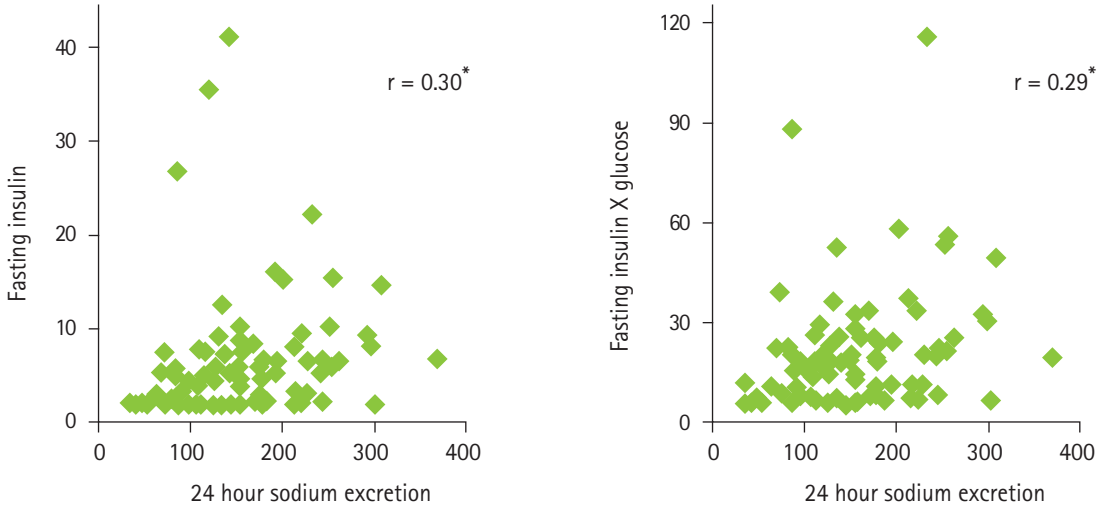

Figure 1. Age- and caloric-adjusted correlation between 24-hour urinary sodium excretion and insulin resistance [36]. *$p < 0.05$.

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low sodium intake decreased insulin resistance salt sensitive individuals the low sodium intake decreased insulin resistance, in salt-resistant individuals [27,33,35,38].

Finally, it seemed that the effect of low sodium intake on insulin resistance also varied according to study population. For example, Perry et al. [20], Donovan et al. [44], and Fliser et al. [22] included only male subjects in their studies. While, Iwaoka et al. [23], Meland M [38] conducted studies only on hypertensive individuals. All participants were diabetes in Petrie JR, and Ames RP's study [24,34].

Recently, Korean Ministry of Food and Drug Safety conducted a correlation study on sodium intake and insulin resistance based on data analysis of 120 subjects using obese and control groups [36]. Sodium consumption was monitored via 24 hour urine collections and 3-day diet records. Results showed correlations between higher sodium consumption and higher blood insulin concentrations and increased insulin resistance. The results were true even after adjusting for age and caloric intake (Figure 1).

Korean Ministry of Food and Drug Safety also conducted a randomized controlled study on 160 obese subjects considering the effects of low-sodium diet on obesity and insulin resistance. In this study, an intervention group of 80 obese subjects were provided with low-sodium (2 g/day) diet for 2 months, and 5 g/day of usual sodium intake was provided to controls. All meals were delivered to participants. Total daily calorie intake, body mass index, and sex were same in both groups. The intervention group showed improved blood pressure, fasting blood glucose, and insulin resistance. The results showed that the low-sodium diet could improve not only blood pressure, but also the level of fasting blood glucose and insulin resistance [36]. This study being the first large-scale randomized controlled study is a quite reliable source of data for scientific analysis as it carefully overcomes the above mentioned limitations in previous studies.

Although, the study overcomes the mentioned limitations; however, the underlying mechanism of the association between insulin resistance and low sodium intake should be further clarified. The following hypotheses have been raised to address the mechanism. First, high sodium intake raises blood leptin levels which result in hypertrophy of abdominal fat cells, which in turn increases the insulin resistance [16]. Second, high sodium diet results in hypertrophy of abdominal fat cells, which in turn is related to blood leptin concentrations [17]. Third, high sodium diet increases insulin resistance by regulating the expression of GLUT4 [18]. Furthermore, there was a study which reports the association between changes in angiotensin II levels and the action of insulin [19].

Conclusion

The current research trend in low sodium intake focuses on the effect of low sodium diet on insulin resistance. Although, many reports have been published additional randomized controlled studies with appropriate experimental validation regarding the potential effects of low sodium diet on obesity and insulin resistance are required. In particular, the test subjects should be categorized by genetic traits regarding sodium sensitivity, and variables including the effect of diet on urine excretion and hormone responses should also be included. In addition, future studies should be adequately long and should be based on an adequate standardized definition of 'low sodium intake' near 2 g.

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