The Effect of Sucralose on 2-hour Postprandial Glucose and Insulin Levels in Non-diabetic Overweight Subjects

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ABSTRACT

Sucralose is an artificial non-caloric sweetener, which is approximately 600 times as sweet as sucrose. Nowadays using of sucralose is not only increasing as foods and drinks additives, but also in pharmaceuticals industries. Because of its non-caloric sweetening property, it is also widely used in weight lossprograms as non-caloric sweeteners found in foods, beverages or snacks. Whereas worldwide consumptions of non-caloric sweetener such as sucralose are rising up, the number of overweight people is also still increasing. This is the question for this study, which purposes to study acute effect of sucralose on glucose homeostasis, focusing on plasma glucose and insulin levels in Thai non-diabetic overweight subjects.

Target population of the researchwas emphasized on overweight participants. Because of characteristics of overweight people, they are likely to have chance to choose a kind of artificial sweetener such as sucralose to use in their daily life, and probability to have some degree of metabolic disorder. However one of inclusion criteria is to have fasting insulin level less than 7 uIU/ml to reduce confounding effect to glucose homeostasis, causing difficult and unreliable interpretation.

Objective —To study acute effect of sucralose on 2-hour postprandial glucose and insulin levels in Thai non-diabetic overweight subjects

Materials and Methods— Experimental clinical trial in 7 non-diabetic overweight subjects (3 men and 4 women aged 29.57±5.68 years), meanBMI=26.1±0.7 Kg/m^2, normal fasting plasma glucose and insulin levels. Each subject was assigned for 4 visits (screening, control condition, experimental conditionand follow up).

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Fasting plasma glucose level, fasting plasma insulin level, 2-hour 75-gram oral glucose tolerance test (75g OGTT) and 2-hour postprandial plasma insulin level were measuredand analyzed. After screening test, subjects who could pass the inclusion criteria will be submitted for the further study.At first visit, after over-night fasting, a blood sample was taken for fasting plasma glucose and fasting plasma insulin level. Then 75g OGTT was performed. At time 120 minutes, blood sample was taken for 2-hour postprandial plasma glucose and insulin levels. For the third visit (experimental condition), after over-night fasting, blood test for fasting plasma glucose and fasting plasma insulin levels were taken. Then 750 mg sucralose was administered orally 30 minutes before 75g OGTT performed. After 75g OGTT, at time 120 minutes, blood test for 2-hour postprandial plasma glucose and insulin levels were measured. The results were statistically analyzed by percentage, mean ± SD and Paired t-test analysis.

Results —In control condition,mean fasting plasma glucose level and fasting plasma insulin level were 91.9±3.6 mg/dL and 4.5±0.9 uIU/mL, respectively. 2-hour postprandial (after 75g OGTT) plasma glucose and insulin levels were 88.9±17.6 mg/dL and 39.8±17.7 uIU/mL. At time 120 minutes after ingestion of 75-gram glucose, insulin levels were statistically increased (P=0.002), but plasma glucose decreased when compared to fasting plasma glucose level (fasting

plasma glucose level and 2-hour postprandial plasma glucose level were 91.9±3.6 mg/dL and 88.9±17.6 mg/dL, respectively) (P=0.602). As for experimental condition (sucralose was used as a test substance), mean fasting plasma glucose and insulin levels were 91.9±7.3 mg/dL and 5.5±1.4 uIU/mL, respectively. At time 120 minutes after 75-gram glucose ingestion, mean insulin level increased significantly (34.6±18.0 uIU/mL) from fasting state (5.5±1.4 uIU/mL) (P=0.005), whereas 2-hour postprandial plasma glucose level was significant lower than fasting plasma glucose at 120minutes (81.6±14.3 mg/dL and 91.9±7.3 mg/dL, respectively) (P=0.44). When experimental condition wascompared to the control, plasma glucose andinsulin levels did not show significant changes at time of 120 minutes (P=0.184 and 0.381, respectively)

Conclusion — 750mg Sucralose did not increase postprandial plasma glucose and insulin levels at time of 120 minutes after 75g oral glucose tolerance test in Thai non-diabetic overweight subjects, when compared to the control condition. No serious adverse event was found after oral sucralose administration at the testdose. Significant reduction in 2-hour postprandial plasma glucose in experimental condition, using sucralose as test substance, needs further study in a future large-scale and long term trial.

Keywords— Sucralose/Artificial sweetener/Plasma glucose level/Blood sugar level/Insulin level/Overweight/Non-diabetic

INTRODUCTION

Humans can perceive sweetness via taste receptors in T1R family (T1R2/T1R3) in the taste buds on the tongue (Zhang, Klebansky, Fine,Liu, Xu, Servant, Zoller, Tachdjian& Li, 2010). Sucralose is classified as second generationchlorinated sugar compound (Weihrauch& Diehl, 2004), which is non-nutritive non-caloric artificial sweetener (Zhao & Johnson, 2000). Sucralose is approximately 600 times as sweet as glucose(Rodero, A. B., Rodero, L. S. &Azoubel, 2009), twice as sweet as saccharin, three times as sweet as aspartame.It has stability under heat and various pH conditions. Today sucralose can be found in foods (as food additive), beverages or even in pharmaceutical industries (Rodeo et al., 2009). Sucralose is not only as a sugar substitute but also medication for a certain disease, such as burning mouth syndrome (BMS) (Hirsch, Ziad, Kim, Lail& Sharma, 2011).Because of sweetness withhypocaloric property, nowadays, sucralose is widely used as sugar substitution in weight loss programs and many weight loss products to reduce daily calorie intake. In contrast, overweight and obese populations are now rising up over time after sugar substitutions are widely used (Yang, 2010). In many studies had shown, in mice, sucralose can stimulate pancreatic beta-cell functions to release hormone (Nakagawa, Nagasawa, Yamada, Hara, Mogami, Nikolaev, Lohse, Shigemura, Ninomiya& Kojima, 2009), such as insulin. Insulin is one of the pancreatic hormones, which plays role in lowering plasma glucose level (hypoglycemic effect), and another islipogenesis effect. So in mice, Martinez, González, García, Salas, Constantino-Casas, Macías, Gracia, Tovar &Durán-de-Bazúa (2010) study results had shown the fatter mice in a group of hypocaloric-sweetener (aspartame and sucralose) feeding. The study suggested mice body mass might be affected with those artificial sweetener. In vivo, some studies had shown no effects on plasma glucose, plasma insulin level (Fujita, Wideman, Speck, Asadi, King, Webber, Haneda&Kieffer, 2009), incretin hormones (Wu, Zhao, Bound, Checklin, Bellon, Little, Young, Jones, Horowitz &Rayner, 2012),gastric emptying time (Ma, Bellon, Wishart, Young, Blackshaw,Jones, Horowitz &Rayner, 2009),appetite, as well energy intake (Ford, Peters, Martins, Sleeth, Ghatei, Frost & Bloom, 2011). On the contrary, recent study,Pepino, Tiemann, Patterson, Wice and Klein (2013)had studied effects of sucralose on plasma glucose and insulin levels. The results were significant increase of peak plasma glucose concentrations (P=0.03), greater increment in insulin area under the curve (P<0.03), greater peak insulin secretion rate (P=0.04), decrease in insulin clearance (P=0.04) and decrease in insulin sensitivity (P=0.01). For this reason, it is

interesting to study the effects of sucralose and plasma glucose and insulin levels in Thai non-diabetic overweight subjects.

OBJECTIVES

To study acute effect of 750 mgsucralose on plasma glucose and insulin levels in Thai non-diabetic overweight subjects

RESEARCHDESIGN AND METHODS

The study wasexperimental clinical trial. Subjects were recruited and underwent screening tests. Subjects who passed the screening tests and inclusion criteria were enrolled to the further study. Seven subjects (3 men and 4 women) were submitted to the study. They were withoverweight, non-diabetic state, age between 20-37 years (mean age of 29.57±5.68 years), mean height of 164.3±8.4cm, mean weight of 70.5±7.5 kg and mean body mass index (BMI) of 26.1±0.7kg/m^2

The inclusion criteria were : voluntary male or female, aged 20-45 years, fasting plasma glucose< 110 mg/dL, fasting insulin level < 7 uIU/mL.

The exclusion criteria were: sucralose consumption within 6 months prior to the study, diseases or disorders that could be unsafe to be participants (i.e. DM, pre-DM, insulin resistance, thyroid, kidney, liver, adrenal glands, cardiovascular disease, cerebrovascular disease, seizure, cancer, psychosis) or might interfere the study results interpretation, use of steroid, drugs or supplements that could affect either plasma glucose or insulin levels, pregnancy and lactation.

Before the study performed, all the participants had undergone medical history record and physical examination. Vital signs were recorded. Blood sample was taken for screening laboratory tests (fasting plasma glucose, plasma insulin level, kidney function test and liver function test). Each subject was assigned for next three visits, which was one week apart.

Second visit (Control condition): Subjects had been fasted overnight. At 6.00 a.m., blood tests for fasting plasma glucose and insulin levels were taken. 75g OGTT was performed, and at time 120 minutes, blood sample was done for 2-hour postprandial plasma glucose and insulin levels test. Adverse events were closely observed.

Third visit (Experimental condition): Subjects were fasted overnight. At6.00 a.m., blood tests for fasting plasma glucose and insulin levels were taken. 750 mg sucralose (contained in 2 opaque capsules) were administered orally 30 minutes prior to 75g OGTT. At 120 minutes, blood sample was done for 2-hour postprandial plasma glucose and insulin levels test. Adverse events were closely observed.

Fourth visit (Follow up):This visit was the study summary declaration to all participants, and the adverse effects from the study would berecorded.

STATISTICAL ANALYSIS

Data were statistically analyzed using percentages, means and standard deviations for descriptive data. Differences between control and experimental condition were analyzed by Paired t-test analysis (95% level of confidence, P value = 0.05).

RESULTS

The general characteristics of participants were 7 subjects submitted to the study, composing of 3 men and 4 women, with a mean age of 29.57±5.68 years, mean height of 164.3±8.4 cm, mean weight of 70.5±7.5 kg, and mean body mass index (BMI) of 26.1±0.7 kg/m^2.

Other from screening and follow-up visits, the study was designed for 2 sessions, the control and experimental condition. 750 mg sucralose was use as a test substance. Blood samples were taken frommedian cubital veinfor fasting plasma glucose levels, fasting plasma insulin levels, 2-hour postprandial plasma glucose levels, and 2-hour postprandial insulin levels. 75g oral glucose tolerance test was performed to evaluate 2-hour postprandial plasma glucose and insulin levels.

Control condition: After subjects had been fasted overnight, blood samples were collected in the next morning for fasting plasma glucose and insulin levels (the results were 91.9±3.6 mg/dL and 4.5±0.9 uIU/mL, respectively), then 75g OGTT was performed (Table 1). At time 120 minutes, Blood samples were taken for 2-hour postprandial plasma glucose and insulin levels, which were88.9±17.6 mg/dL and 39.8±17.7 uIU/mL (Fig. 1 and Fig. 2). There was significant increase of insulin level after 75g OGTT (at time 120 minutes, P=0.002). In contrast, 2-hour postprandial plasma glucose level was lower than fasting plasma glucose level, 88.9±17.6 mg/dL and 91.9±3.6 mg/dL (P=0.602)(Fig. 3,Table 2 and Table 3).

Table 1— Fasting plasma glucose and insulin levelsand 2-hour postprandial plasma glucose and insulin levels, after 75g glucose administration (75g OGTT)

Subjects	Fasting Plasma Levels		2-hour Postprandial Plasma Levels (2-hour after 75g OGTT)	
	Plasma Glucose Levels (mg/dL)	Plasma Insulin Levels (uIU/mL)	Plasma Glucose Levels (mg/dL)	Plasma Insulin Levels (uIU/mL)
1	87	6	80	41.9
2	93	4.6	96	35.4
3	90	3.8	74	71.7
4	90	5	73	22.8
5	97	4.2	111	53.9
6	96	4.9	113	28.3
7	90	3.1	75	24.9
$\bar{x}$ =	91.9	4.5	88.9	39.8
S.D. =	3.63	.93	17.64	17.72

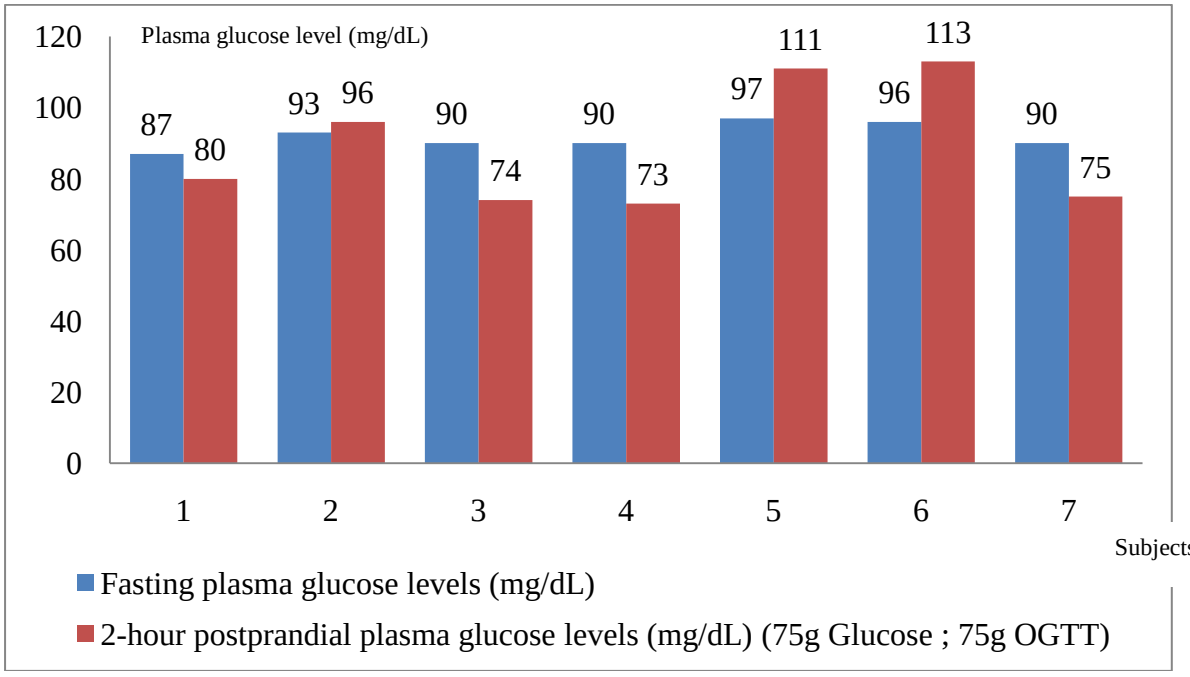

Figure 1— Comparison of fasting plasma glucose levels versus 2-hour postprandial plasma glucose levels in seven subjects individually.

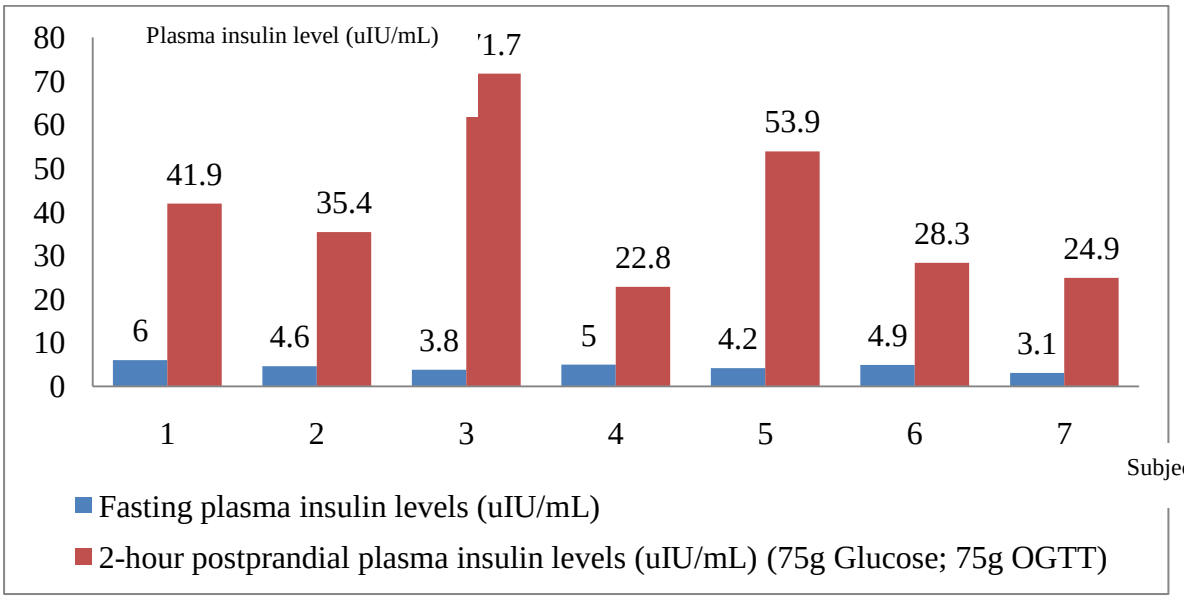

Figure 2— Comparison of fasting plasma insulin levels versus 2-hour postprandial plasma insulin levels in seven subjects individually.

Table 2 — Comparison of 2-hour postprandial plasma glucose level versus fasting plasma glucose level in control condition

Test	n	$\bar{x}$	S.D	t-test	P.
Fasting plasma glucose level	7	91.9	3.6	.550	.602
2-hour postprandial plasma glucose level (75g Glucose; 75g OGTT)	7	88.9	17.6		

Table 3 — Comparison of 2-hour postprandial plasma insulin level versus fasting plasma insulin levelin control condition

Test	n	$\bar{x}$	S.D	t-test	P.
Fasting plasma insulin level (uIU/mL)	7	4.5	.9	5.224	.002*
2-hour postprandial plasma insulin level (75g Glucose; 75g OGTT)	7	39.8	17.7		

Note. * Significant difference at the .05 level

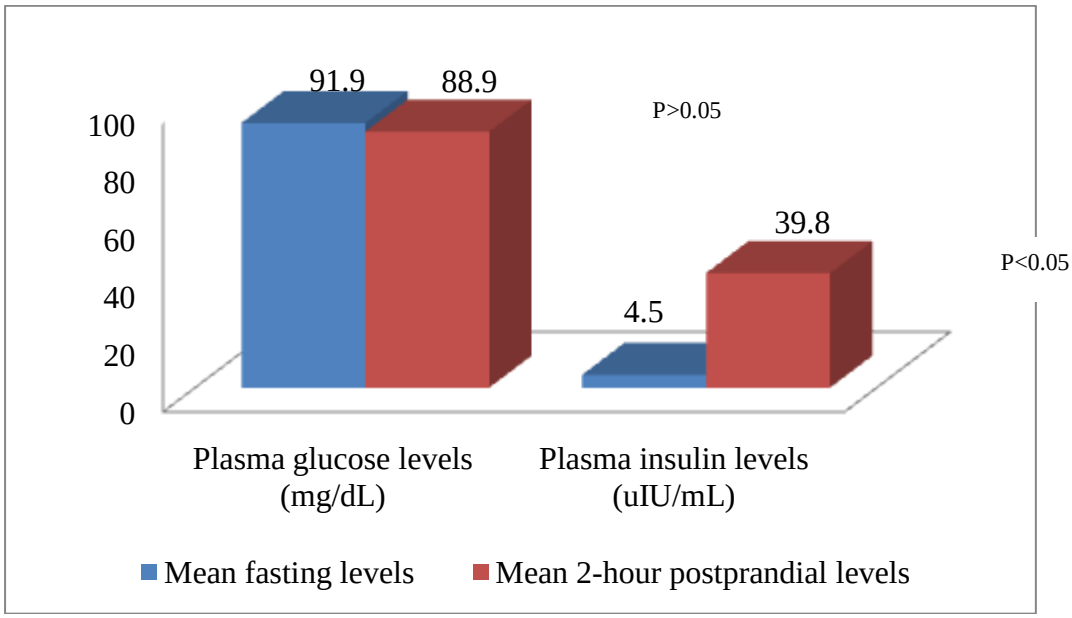

Figure 3—Comparison of mean fasting plasma glucose and insulin levels versus 2-hour postprandial plasma glucose and insulin levels after 75g glucose ingestion (75g OGTT)

Experimental condition: After overnight fasting, fasting blood samples were taken for fasting plasma glucose and insulin levels. Then 750 mg sucralose, containing in two white opaque capsules, were given to all subjects. Sucralose capsules were administered orally 30 minutes before 75g OGTT was performed. Mean fasting plasma glucose level was 91.9±7.3 mg/dL(Fig. 4, Fig. 5 and Table 4). 2-hour postprandial plasma glucose was significant lowered (81.6±14.3 mg/dL) (P=0.044). On the contrary, 2-hour postprandial plasma insulin level was statistically increased from 5.5±1.4 mg/dL (fasting insulin level) to 34.6±18.0 mg/dL (P=0.005) (Fig. 6, Table 5 and Table 6).

Table 4— Fasting plasma glucose and insulin levelsand 2-hour postprandial plasma glucose and insulinlevels, after 750mg Sucralose and 75g glucose administration (75g OGTT)

Subjects	Fasting Plasma Levels		2-hour Postprandial Plasma Levels (2-hour after 750 mg Sucralose + 75g OGTT)	
	Plasma Glucose Levels (mg/dL)	Plasma Insulin Levels (uIU/mL)	Plasma Glucose Levels (mg/dL)	Plasma Insulin Levels (uIU/mL)
1	86	4.9	80	42.1
2	102	2.7	87	12.9
3	90	5.9	76	44.1
4	83	6.7	77	15.1
5	100	6.0	109	64.7
6	95	6.8	80	34.1
7	87	5.7	62	29.1
$\bar{x}$ =	91.9	5.5	81.6	34.6
S.D. =	7.3	1.4	14.3	18.0

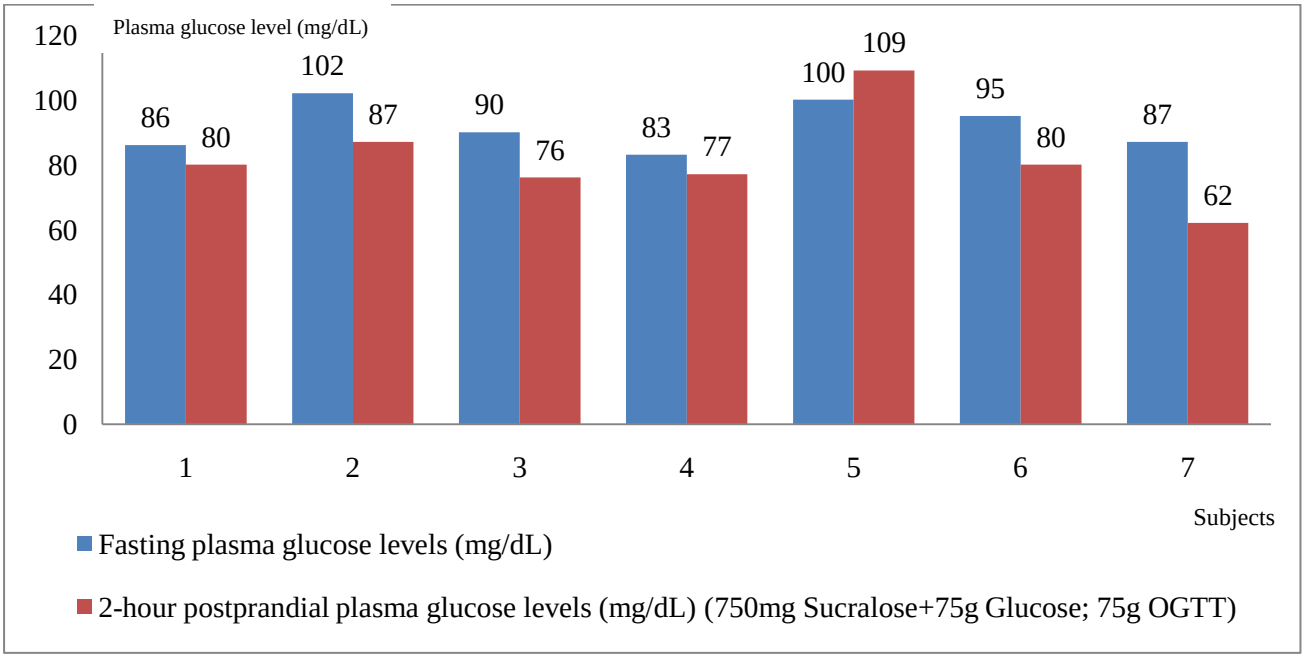

Figure 4 — Comparison of fasting plasma glucose levels versus 2-hour postprandial plasma glucose levels in seven subjects individually (750mg Sucralose + 75g Glucose, 75g OGTT).

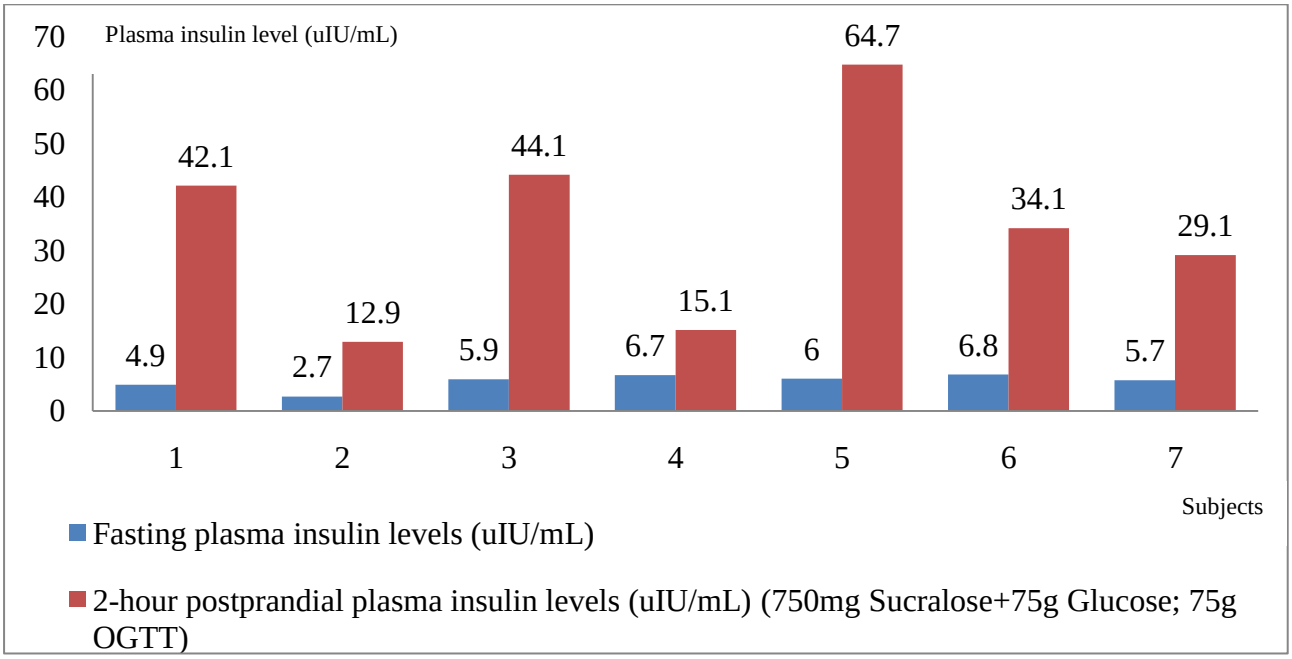

Figure 5 — Comparison of fasting plasma insulin levels versus 2-hour postprandial plasma insulin levels in seven subjects individually (750mg Sucralose + 75g Glucose, 75g OGTT).

Table 5 — Comparison of 2-hour postprandial plasma glucose level versus fasting plasma glucose level in experimental condition (750mg Sucralose + 75g Glucose)

Test	n	$\bar{x}$	S.D	t-test	Sig.
Fasting plasma glucose level (mg/dL)	7	91.9	7.3	- 2.550	.044*
2-hour postprandial plasma glucose level (mg/dL) (750mg Sucralose+75g Glucose; 75g OGTT)	7	81.6	14.3		

Note. * Significant difference at the .05 level

Table 6 — Comparison of 2-hour postprandial plasma insulin level versus fasting plasma insulin level in experimental condition (750mg Sucralose + 75g Glucose)

Test	n	$\bar{x}$	S.D	t-test	Sig.
Fasting plasma insulin level (uIU/mL)	7	5.5	1.4	-4.838	.005*
2-hour postprandial plasma insulin level (uIU/mL) (750mg Sucralose+75g Glucose; 75g OGTT)	7	34.6	18.0		

Note. * Significant difference at the .05 level

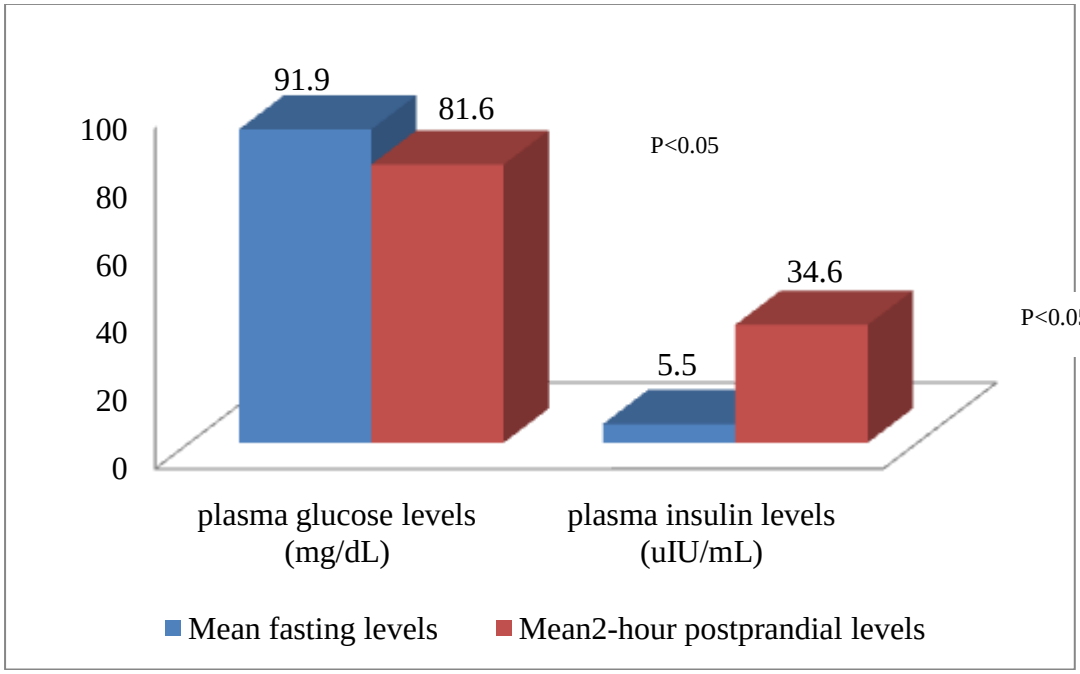

Figure 6— Comparison of mean fasting plasma glucose and insulin levels versus 2-hour postprandial plasma glucose and insulin levels after 750 mg Sucralose + 75g glucose ingestion (75g OGTT)

When experimental condition was compared to the control, plasma glucose levels as well as plasma insulin level did not show significant changes (P=0.184 and P=0.381, respectively) (Fig. 7) for 750 mg sucralose, measured by 75g OGTT.

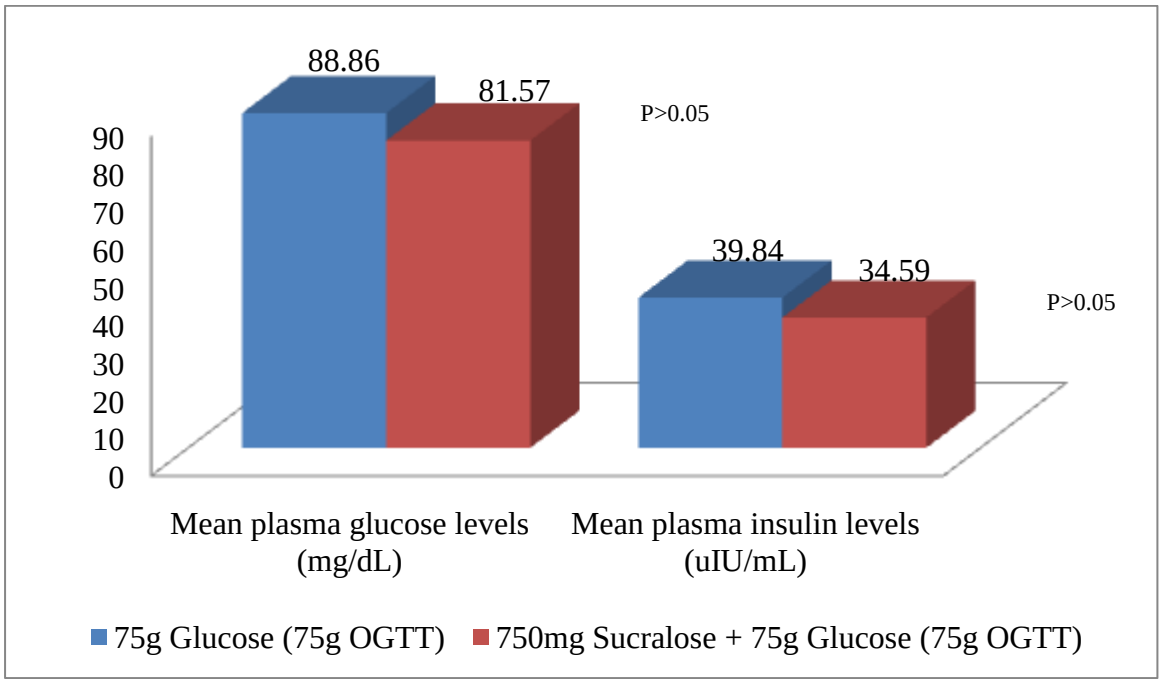

Figure 7 — Comparison between control (75g OGTT) versus experimental condition (750mg Sucralose+75g Glucose; 75g OGTT), demonstrating mean plasma glucose level (mg/dL) and mean plasma insulin level (uIU/mL)

CONCLUSIONS

This research aimed to study acute effect of sucralose on plasma glucose and insulin levels. In spite of difficulty of gathering adequate overweight subjects with fasting insulin level less than 7 uIU/mL (Sung, Seo, Rhee & Wilson, 2011), the study had recruited all subjects by inclusion and exclusion criteria strictly. The results from this study hadshown no significant changes in plasma glucose and insulin levels after 750 mg sucralose administered orally, measured by 75g OGTT at time of 120 minutes, in seven non-diabetic overweight subjects with mean BMI of 26.1±0.7 kg/m^2, mean fasting plasma glucose level of 91.9±3.63 and mean fasting insulin level of 4.5±0.9 uIU/mL.

In two sessions of control and experimental condition, the results had shown significant increase in 2-hour postprandial plasma insulin levels after oral 75g glucose administration, but 2-hour postprandial plasma glucose levels decreased from fasting state. These findings were actions of hypoglycemic hormone such as insulin toreduce postprandial plasma glucose levelsphysiologically.

When the results were analyzed between experimental and the control condition,using paired t-test analysis, neither 75g glucose alone nor preceding with oral sucralose prior to glucose consumption was no significant changes in the 2-hour postprandial plasma glucose and insulin levels by 75g OGTT test. Sucralose did not show ability to increase mean 2-hour postprandial insulin level or plasma glucose levels as well.One of the noticeable findings was, in experimental (sucralose) condition,there was unexpectedly found a significant reduction in mean 2-hour postprandial plasma glucose level when compared to fastinglevel. According to previous study (Mezitis, Maggio, Koch,Quddoos,Allison& Pi-Sunyer, 1996), they had study the effects of single high oral dose of sucralose (1,000 mg) on plasma glucose and insulin levels in patients with diabetes. There were 3 hypoglycemic episodes during the study, but they were not considered as an adverse effect from sucralose administration. So this unexpected finding may require further study.

For adverse events during the study, no serious adverse events of sucralose and glucose consumption was observed and reported.

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