Original Article

Some affecting factors of insulin resistance: Do amounts of adipose tissue and age have independent impact on the development of insulin resistance?

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ABSTRACT

Background: Insulin resistance is a pathophysiological condition in which cells fail to respond normally to insulin. Many studies suggest that amounts of adipose tissue are of the most important risk factors for insulin resistance, also the aging process is usually associated with insulin resistance. Objectives: we decided to perform a study for evaluating these risk factors for insulin resistance in Iranian population. Methods: in cross-sectional study on 1500 Tehran's population, demographic data including age, gender, and menopausal status, blood samples with 12 hours fasting condition, weight, height, wrist circumference, hip and waist collected and recorded by trained person. All the statistical analysis carried out in SPSS and P-value <0.05 considered statistically significant. Results: Out of 1500 participants, 930 (62%) persons were female and 570 (38%) were male. The main variables in our study (age and body adiposity) in men and women correlated significantly with fasting insulin, least correlation was seen for 2h glucose. After using linear regression model, we show that BMI is not related to metabolic variables but body adiposity has strongest association to all metabolic variables. Age has only related to Fasting Blood sugar (FBS) and 2h insulin. Conclusion: The results of our study show that the amounts of body fat, gender and age affect insulin resistance and BMI except fasting insulin does not have a relationship with other variables.

Keywords: Insulin resistance, Body adiposity, Abdominal fat, Aging, BMI.

Introduction

Insulin resistance is a pathophysiological condition in which cells fail to respond normally to the insulin [1, 2]. At the molecular level, PI3K /Akt /mTOR signaling pathway is responsible for creating the message from insulin, and this pathway is disrupted in the process of insulin resistance [3, 4].

Different mechanisms are discussed for insulin resistance. Epidemiological studies suggest that abdominal obesity is one of the most important risk factors for insulin resistance, type 2 diabetes, heart diseases, heart attack, metabolic syndrome and death [5]. Adipose tissue is the main cause of different disorders including metabolic disorders. Adipose tissue is an important place of energy storage that consists of fat cells, extra-cellular matrix, nervous tissue, vessels and other cells types like: pre-adipocytes, fibroblasts, stem cells and also immune cells such as macrophages and lymphocytes. Adipose tissue provides several processes including metabolic homeostasis of the whole body, immunity, inflammatory response, blood coagulation, reproduction, function of endothelial tissue and adipose tissue differentiation [6]. In the past, adipose tissue was considered as a triglycerides storage and releasing tissue but new studies have shown that adipose tissue secretes multiple proteins with the general name adipokines that these proteins play a role in cholesterol metabolism, energy regulation and insulin function; hence, this tissue is a dynamic endocrine unit. Adipose tissue

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can alone regulate insulin sensitivity by different hormonal signals such as signals that come from nervous system; TNF-α, adiponectin and leptin are such hormones [7]. In addition, adipose tissue hormones secrete other molecules including resistin, IL-1 beta that can decrease insulin sensitivity.

The aging process usually leads to an increase in abdominal obesity [8, 9]. However, both lean and obese individuals may have a age related changes in white adipose tissue phenotype that causes changes in energy metabolism and inducing systemic insulin resistance [10]. These changes occur in muscle tissue since the muscle tissue is the main location of insulin receptors it can be important in the development of resistance. Also, the process of age-related increase is associated with an increase in white adipose tissue and disorders in the thermogenesis of brown adipose tissue that both lead to increasing prevalence of obesity and type 2 diabetes. The process of increasing age is associated with the sarcopenia [11]. Age-related sarcopenia with the reduction in lean tissue and physical activity leads to a higher incidence of insulin resistance, type 2 diabetes, dyslipidemia and hypertension. A clear example of such a case is obesity and accumulation of fat in abdominal area that both of them are associated with insulin resistance and other mentioned disorders [12]. Age-associated increase in the prevalence of abdominal obesity and insulin resistance in elderly diabetic patients and also healthy Japanese people has been observed that shows significantly relationship between waist circumference and insulin resistance [1, 8]. There is studies that have shown insulin resistance is independent from the amounts of body fat and increases with age, although there are growing evidences that development of insulin resistance might be associated with abdominal adiposity [5]. Hence, there isn't any consensus on the relationship between insulin resistance and age.

Objectives

In this study, we tried to evaluate the effect of the amounts of body fat and aging on insulin resistance to show is there any independent association between body fat and aging with insulin resistance in Iranian population.

Materials and Methods

This cross-sectional study was conducted on 1500 people of Tehran's population from April to March 2015. Samples were selected randomly in the form of cluster sampling from Tehran. The exclusion criteria of the study were taking medication that affecting blood sugar and insulin. The purpose of the study was explained for subjects and the informed consent was completed by individuals before entering the study.

Demographic data including age, gender, and menopausal status were asked from subjects. Blood samples were collected after a night fasting. Weight and height measured and recorded by trained person. Height was measured by stadiometer with an accuracy of 0.1 cm and the weight was measured by digital balance with an accuracy of 0.1 kg. BMI was calculated through dividing weight in kg to the square of height in meters. Overweight and obesity were defined based on the BMI that we considered. BMI from 25 to 30 as overweight and BMI above 30 was obese. Wrist circumference, hip and waist were measured with an accuracy of 0.1 cm with an inelastic tape measure. Waist circumference at the narrowest part of the waist was measured between tenth ribs and the iliac crest. Hip measurement carried out in a standing position at the most hip circumference.

Blood sample was taken of subjects in 12 hours fasting. The measurement of blood sugar was performed by Pars Azmoon commercial kit. For measuring serum insulin we used R&D Systems DY8056-05 by ELISA method. HOMA-IR as an index for insulin resistance was calculated by using Fasting Blood Sugar (FBS) and insulin concentration by HOMA CALCULATOR software (v 2.2).

The amount of body fat was measured by (GE Healthcare ™) DEXA method. Evaluated by scanning the whole body, two hands, two legs and trunk. Trained personnel performed this test.

Descriptive statistics performed using mean (SD) and frequency (percent) for quantitative and qualitative variables respectively. Independent T test and Chi square test were implemented as univariate statistical tests and multiple linear regression as multivariate test. All the statistical analysis carried out in SPSS version 16.0 and P-value <0.05 considered statistically significant.

Results

Out of 1500 participants, 930 (62%) persons were female and 570 (38%) were male. Males and females had significant difference in term of age, weight and most of metabolic indices except FBS (107.14 vs 107.51, P=0.67) and HOMA B (73.2 vs 72.34) (Table 1). Apart from FBS, in other metabolic parameters there was a significant difference between men and women.

Table 1: demographic and metabolic variables

Variable	Total (1500)	Male (570)	Female (930)	P-value
Age (year)	44 (15)	40.02 (11.54)	41.42 (11.58)	0.023
Weight (kg)	87.78 (14.57)	86.61 (14.28)	88.50 (14.72)	0.015
Height (cm)	162.68 (12.70)	166.21 (12.83)	160.51 (12.12)	<0.001
BMI	27.89 (4.73)	27.35 (4.60)	28.22 (4.78)	<0.001
WC (cm)	105.44 (18.57)	100.90 (14.68)	108.22 (20.09)	<0.001
Wirst (cm)	16.45 (1.29)	16.64 (1.26)	16.34 (1.28)	<0.001
Hip ratio (cm)	107.10 (12.19)	104.88 (11.43)	108.47 (12.45)	<0.001
WHR	0.98 (0.12)	0.96 (0.10)	1.00 (0.14)	<0.001

WHtR	0.65 (0.13)	0.61 (0.10)	0.68 (0.13)	<0.001
FBS (mg/dL)	107.37 (16.58)	107.14 (16.11)	107.51 (16.87)	0.67
Fast insulin	10.60 (4.70)	10.29 (4.71)	10.79 (4.69)	0.044
2 hour glucose (mg/dL)	121.14 (20.98)	115.8 (20.28)	124.4 (20.73)	<0.001
2 hour insulin	45.81 (14.28)	49.23 (14.46)	43.71 (13.76)	<0.001
HOMA IR	1.03 (0.26)	1.09 (0.27)	0.99 (0.25)	<0.001
HOMA B	72.67 (18.08)	73.20 (17.77)	72.34 (18.27)	0.37
Total fat (gr)	28343.84 (11497.95)	27167.59 (11287.92)	29064.77 (11571.82)	0.002
Frame size		10.04 (1.08)	9.89 (1.08)	0.005
Smoking	Yes	124 (21.8)	52 (5.6)	<0.001
	No	446 (78.2)	878 (94.4)	
Frame size	Small	191 (33.5)	154 (16.6)	<0.001
	Medium	181 (31.8)	225 (24.2)	
	Large	198 (34.7)	551 (59.2)	
BMI	Normal	194 (34.0)	271 (29.1)	0.11
	Over weight	171 (30.0)	314 (33.8)	
	Obese	205 (36.0)	345 (37.1)	
Waist	Normal	197 (34.6)	106 (11.4)	<0.001
	Obese	373 (65.4)	824 (88.6)	

BMI: Body mass index, WC: waist circumference, WHR: Waist to hip ratio, WHtR: Waist to height ratio, FBS: Fasting blood sugar.

In Table 2, the correlation between variables measured in this study have shown together. The main variables in our study (age and body adiposity) has a significant correlation with all of the variables studied, such as fasting glucose, 2h glucose or fasting insulin in both men and women. In women, age has the highest relationship with abdominal fat (r=0.944, p<0.001) and in metabolic variables, most correlated variable was fasting insulin (r=0.872, p<0.001) and the lowest correlation was seen by 2h glucose (r=0.447, p<0.001). Abdominal fat and total fat both has the highest correlation in metabolic variables with fasting insulin (r=0.913 and 0.916 respectively, p<0.001) and lowest correlation with 2h glucose (r=0.461 in both, p<0.001).

A similar pattern was seen in men but with the difference, that total body fat correlation with age was slightly higher than abdominal fat (0.957 vs 0.953) and in metabolic variables also fasting insulin had the highest correlation (r = 0.889, p <0.001) and 2h glucose showed the lowest correlation (r = 0.619, p <0.001). For abdominal fat and total fat most correlation like women was seen by fasting insulin (r=0.918, 0.921 respectively, p<0.001) and least correlation was seen for 2h glucose (r=0.633, 0.641 respectively, p<0.001).

In order to access the simultaneous effect of BMI, age, sex and total body fat on metabolic parameters, multiple regression with enter method performed. Table 3 shows clearly that the total for every five components can have a significant effect. Age only for FBS and 2h insulin has a significant impact after adjusting sex, BMI and total body fat. Reported R squares in table 3 reveal that considered factors could explain 74 and 84 percent of variability in FBS and fast insulin respectively that is significant value.

Table 2. Correlation matrix among anthropometric indices with metabolic variables

		Age	BMI	WC	Trunk Fat	Total Fat	FBS	Fast_Insulin	2h_Glucose	2h_ Insulin	HOMA_ IR		
Male	Age	1	.814**	.881**	.944**	.942**	.813**	.872**	.447**	.675**	.640**	Age	Female
	BMI	.835**	1	.797**	.850**	.843**	.739**	.791**	.405**	.609**	.559**	BMI	
	WC	.817**	.777**	1	.918**	.909**	.792**	.846**	.437**	.644**	.606**	WC	
	Trunk Fat	.953**	.875**	.844**	1	.981**	.860**	.913**	.461**	.705**	.658**	Trunk Fat	
	Total Fat	.957**	.865**	.840**	.987**	1	.857**	.916**	.461**	.695**	.652**	Total Fat	
	FBS	.811**	.749**	.709**	.847**	.858**	1	.806**	.432**	.648**	.554**	FBS	
	Fast_Insulin	.889**	.803**	.780**	.918**	.921**	.803**	1	.443**	.651**	.589**	Fast_Insulin	
	2h_Glucose	.619**	.578**	.525**	.633**	.641**	.558**	.590**	1	.371**	.285**	2h_Glucose	
	2h_Insulin	.712**	.643**	.605**	.733**	.738**	.662**	.673**	.458**	1	.461**	2h_Insulin	
	HOMA_IR	.633**	.578**	.563**	.676**	.660**	.581**	.616**	.394**	.477**	1	HOMA_IR	

BMI: Body mass index, WC: waist circumference, FBS: Fasting blood sugar.

*.p < 0.05.

**.p < 0.001.

Table 3, relationship between blood sugar homeostatic variables by most known risk factors

	FBS (mg/dL) $R^2 = 0.74$		Fasting Insulin $R^2 = 0.84$		2h Glucose $R^2 = 0.31$		2h Insulin $R^2 = 0.52$		HOMA-IR $R^2 = 0.45$	
	β *	P	β *	P	β *	P	β *	P	β *	P
Age	0.08	0.02	0.02	0.44	0.04	0.44	0.10	0.04	0.09	0.09
Sex (Female)	-0.06	<0.001	-0.2	0.03	0.16	<0.001	-0.24	<0.001	-0.25	<0.001
BMI	0.04	0.10	0.05	0.02	0.07	0.11	0.05	0.15	0.02	0.55
Total Fat (gr)	0.75	<0.001	0.86	<0.001	0.42	<0.001	0.57	<0.001	0.55	<0.001

Discussion

The results of our study show that the amounts of body fat, gender and age affect insulin resistance but, BMI except fasting insulin affects the other parameters. We used five indexes for investigating insulin resistance including: FBS, fasting insulin, 2 hours glucose, 2 hours insulin and HOMA-IR. We showed that BMI effect on insulin resistance contrary to most of the studies that emphasize on its major impact on insulin resistance, has not a significant role in insulin resistance pathogenesis and probably exert its effect through increasing the amounts of adipose tissue on insulin resistance.

Insulin resistance is one of the early signs of metabolic resistance [13]. Our study supports this hypothesis that body fat levels have a role in insulin resistance and this relationship is significant despite the removal of other factors such as age, sex and BMI that usually in studies are named as risk factors of insulin resistance. The study by Ling et al is consistent with the results of this study [14]. Also, Bassali et al found the similar results in relation of the abdominal circumference and insulin resistance [15]. It seems that increasing body fat levels can be a start for metabolic diseases such as metabolic syndrome which causes increase in cardiovascular diseases and increase mortality risk [16].

FBS is one of the most important health parameters in the human body that attention to it can reduce the incidence and prevalence of life-threatening diseases [17]. The results of our study showed that increasing in age, female gender and body fat increase FBS level. These results are consistent with Bragg et al, in age and body fat variable but they are in contrast with the results of gender [17]. In a study, McLaughlin et al states that age, sex, body fat level and BMI increase insulin resistance and blood glucose level that in some variables are in line with our study and in some variables are in contrast [18]. Given that the BMI is calculated by dividing the weight by the square of the height and the body weights consists of fat tissues, maybe this is the cause of finding direct relationship between BMI and insulin resistance in McLaughlin study. It seems that, according to the impact of body weight in the equation of BMI, in those who have a high body weight but are low in fat (such as athletes), this assumption of McLaughlin study is not true. However, our study shows that if we consider only the adipose tissue, it has a strong impact on insulin resistance. In line with our study results, Gannage et al and some other studies showed that BMI was not associated with metabolic syndrome and insulin resistance and there is independency [19-21]. In a study, Martin et al found that there was a direct relationship between leptin, adipose tissue levels, obesity and increasing blood insulin and insulin resistance amounts [22].

Another interesting aspect of our study was the relationship of age and insulin resistance even after adjusting for variables such as BMI and body fat level, had a significant role in fasting glucose and 2 hours insulin. Although, several studies disagree with this interpretation and from their perspectives, more important factors than age are effective in insulin resistance or by removing their effects, the relationship between age and insulin resistance disappears [23-25]; but there are studies that showed aging process is associated with insulin resistance. As an example, in a study of Fink et al showed reducing in oral glucose tolerance test in an elderly population and evaluating insulin levels against increased level of glucose states an insulin resistance condition that it has been an unclear relationship by the name of elderly induced insulin resistance [26]. In another study, by Ligen Lin et al, were found that age has relationship with obesity and insulin resistance [27] that were the same as results by Takashi Sakuria et al, showed that aging increases the prevalence of abdominal obesity and insulin resistance [1].

In another study conducted by Helen Karakelides et al demonstrated that increasing age from fourth decade has an increasing role in sarcopenia and changing hormone levels that increases the prevalence of insulin resistance [12]. Kohrt et al showed that insulin resistance independent of total fat changes, increase with aging [5] while, in another study by Ervin Szoke et al in 2008 stated that aging didn't have direct effect on insulin sensitivity independent of changes in body composition [28]. Magdalena Jura and colleagues conducted a study in 2016 shows that increased visceral fat was a key contributor to insulin resistance and metabolic syndrome [10]. Their search was that obesity triggers adipose tissue inflammation during aging, resulting in insulin resistance. In a study Nir Brazilia et al in 1998 found that aging is associated with progressive increase in fasting insulin levels and visceral adiposity in humans and animal models [29]. Francesca Amati et al in 2009 found that during aging, obesity and physical inactivity leads to insulin resistance [30] that were Similar to the findings of Ilangabrirly et al., Found that the removal of visceral fat prevents insulin resistance and glucose intolerance during aging [25].

From the limitations of current study, can be mentioned to the lack of studying on more confounding factors such as: socioeconomic status, nutrition, physical activity and aerobic exercises that have not been examined. Our study suggests that study factors should be investigated in larger populations as well as in longitudinal studies, the severity of the effects of the variables discussed is carefully examined.

Conclusion

According to the present study, we found that gender and the amounts of adipose tissue and age are effective on insulin resistance levels or sensitivity to it. This finding means that body fat levels regardless of weight can induce insulin resistance. Therefore, it is better in future studies and as well as in policy making pay more attention to the controlling body fat levels also, assessment methods for body fat levels should be considered for screening the metabolic diseases risks like insulin resistance, diabetes and heart diseases.

Conflict of Interest:

There is no conflict of interest to be declared regarding the manuscript.

Implication for health policy makers/practice/research/medical education:

Determining the relationship between metabolic homeostatic indices with age and body adiposity can help policy makers for designing preventive programs for diabetes or metabolic syndrome that cause about the loss of a yearly 19.7 million daily adjusted life years. The results of present study shows body adiposity is major determinant of insulin resistance and we must pay more attention to controlling adiposity in community.

References

1. Sakurai T, Iimuro S, Araki A, Umegaki H, Ohashi Y, Yokono K, et al. Age-associated increase in abdominal obesity and insulin resistance, and usefulness of AHA/NHLBI definition of metabolic syndrome for predicting cardiovascular disease in Japanese elderly with type 2 diabetes mellitus. Gerontology. 2009;56(2):141-9.
2. Zand H, Homayounfar R, Cheraghpour M, Jeddi-Tehrani M, Ghorbani A, Pourvali K, et al. Obesity-induced p53 activation in insulin-dependent and independent tissues is inhibited by beta-adrenergic agonist in diet-induced obese rats. Life sciences. 2016;147:103-9.
3. Wang G. Singularity analysis of the AKT signaling pathway reveals connections between cancer and metabolic diseases. Physical biology. 2010;7(4):046015.
4. Homayounfar R, Jeddi-Tehrani M, Cheraghpour M, Ghorbani A, Zand H. Relationship of p53 accumulation in peripheral tissues of high-fat diet-induced obese rats with decrease in metabolic and oncogenic signaling of insulin. General and comparative endocrinology. 2015;214:134-9.
5. Kohrt WM, Kirwan JP, Staten MA, Bourey RE, King DS, Holloszy JO. Insulin resistance in aging is related to abdominal obesity. Diabetes. 1993;42(2):273-81.
6. Babai MA, Arasteh P, Hadibarhaghtalab M, Naghizadeh MM, Salehi A, Askari A, et al. Defining a BMI cut-off point for the Iranian population: the Shiraz Heart Study. PloS one. 2016;11(8):e0160639.
7. Ehrampoush E, Homayounfar R, Davoodi SH, Zand H, Askari A, Kouhpayeh SA. Ability of dairy fat in inducing metabolic syndrome in rats. SpringerPlus. 2016;5(1):2020.
8. Hirose H, Takayama M, Iwao Y, Kawabe H. Effects of aging on visceral and subcutaneous fat areas and on homeostasis model assessment of insulin resistance and insulin secretion capacity in a comprehensive health checkup. Journal of atherosclerosis and thrombosis. 2016;23(2):207-15.
9. Ehrampoush E, Arasteh P, Homayounfar R, Cheraghpour M, Alipour M, Naghizadeh MM, et al. New anthropometric indices or old ones: Which is the better predictor of body fat? Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2016.
10. Jura M, Kozak LP. Obesity and related consequences to ageing. Age. 2016;38(1):1-18.
11. Sczelecki S, Besse-Patin A, Abboud A, Kleiner S, Laznik-Bogoslavski D, Wrann CD, et al. Loss of Pgc-1α expression in aging mouse muscle potentiates glucose intolerance and systemic inflammation. American Journal of Physiology-Endocrinology and Metabolism. 2014;306(2):E157-E67.
12. Karakelides H, Nair KS. Sarcopenia of aging and its metabolic impact. Current topics in developmental biology. 2005;68:123-48.
13. Ziaee A, Esmailzadehha N, Oveisi S, Ghorbani A, Ghanei L. The threshold value of homeostasis model assessment for insulin resistance in Qazvin Metabolic Diseases Study (QMDS): assessment of metabolic syndrome. Journal of research in health sciences. 2015;15(2):94-100.
14. Ling JCY, Mohamed MNA, Jalaludin MY, Rampal S, Zaharan NL, Mohamed Z. Determinants of High Fasting Insulin and Insulin Resistance Among Overweight/Obese Adolescents. Scientific Reports. 2016;6.
15. Bassali R, Waller JL, Gower B, Allison J, Davis CL. Utility of waist circumference percentile for risk evaluation in obese children. International Journal of Pediatric Obesity. 2010;5(1):97-101.
16. McCarty MF. Poor vitamin D status may contribute to high risk for insulin resistance, obesity, and cardiovascular disease in Asian Indians. Medical hypotheses. 2009;72(6):647-51.
17. Bragg F, Li L, Smith M, Guo Y, Chen Y, Millwood I, et al. Associations of blood glucose and prevalent diabetes with risk of cardiovascular disease in 500 000 adult Chinese: the China Kadoorie Biobank. Diabetic Medicine. 2014;31(5):540-51.
18. McLaughlin T, Lamendola C, Coghlan N, Liu T, Lerner K, Sherman A, et al. Subcutaneous adipose cell size and distribution: relationship to insulin resistance and body fat. Obesity. 2014; 22(3):673-80.
19. Gannagé-Yared M-H, Khalife S, Semaan M, Fares F, Jambart S, Halaby G. Serum adiponectin and leptin levels in relation to the metabolic syndrome, androgenic profile and somatotropic axis in healthy non-diabetic elderly men. European Journal of Endocrinology. 2006; 155(1):167-76.

20. Santaniemi M, Kesäniemi YA, Ukkola O. Low plasma adiponectin concentration is an indicator of the metabolic syndrome. European Journal of Endocrinology. 2006; 155(5):745-50.
21. Baratta R, Amato S, Degano C, Farina MG, Patanè G, Vigneri R, et al. Adiponectin relationship with lipid metabolism is independent of body fat mass: evidence from both cross-sectional and intervention studies. The Journal of Clinical Endocrinology & Metabolism. 2004; 89(6):2665-71.
22. do Carmo Martins M, Faleiro LL, Fonseca A. Relationship between leptin and body mass and metabolic syndrome in an adult population. Revista Portuguesa de Cardiologia (English Edition). 2012;31(11):711-9.
23. Basu R, Breda E, Oberg AL, Powell CC, Dalla Man C, Basu A, et al. Mechanisms of the age-associated deterioration in glucose tolerance. Diabetes. 2003; 52(7):1738-48.
24. Ferrannini E, Vichi S, Beck-Nielsen H, Laakso M, Paolisso L, Smith G, et al. Insulin action and age: European Group for the Study of Insulin Resistance (EGIR). Diabetes. 1996;45(7):947-53.
25. Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, et al. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging. Diabetes. 2002; 51(10):2951-8.
26. Fink RI, Kolterman OG, Griffin J, Olefsky JM. Mechanisms of insulin resistance in aging. Journal of Clinical Investigation. 1983;71(6):1523.
27. Lin L, Saha PK, Ma X, Henshaw IO, Shao L, Chang BH, et al. Ablation of ghrelin receptor reduces adiposity and improves insulin sensitivity during aging by regulating fat metabolism in white and brown adipose tissues. Aging cell. 2011;10(6):996-1010.
28. Szoke E, Shrayyef MZ, Messing S, Woerle HJ, Van Haeften TW, Meyer C, et al. Effect of aging on glucose homeostasis. Diabetes Care. 2008;31(3):539-43.
29. Barzilai N, Banerjee S, Hawkins M, Chen W, Rossetti L. Caloric restriction reverses hepatic insulin resistance in aging rats by decreasing visceral fat. Journal of Clinical Investigation. 1998; 101(7):1353.
30. Amati F, Dubé JJ, Coen PM, Stefanovic-Racic M, Toledo FG, Goodpaster BH. Physical inactivity and obesity underlie the insulin resistance of aging. Diabetes care. 2009;32(8):1547-9.