Insulin-Like Growth Factor 1 (IGF- 1) Levels And Left Ventricular Meridional End Systolic Stress (LVMESS) Interrelationship In Middle- Aged And Elderly Obese Subject With Type 2 Diabetes Mellitus

الترابط بين عامل النمو الذي يشبه الأنسولين (IGF-1) وإجهاد البطين الأيسر الانقباضي للألياف الطوليه (LVMESS) في الفئة العمرية المتوسطة وكبار السن الذين يعانون من السمنة المفرطة ومرض السكري النوع الثاني.

Khalid Amber(FACC, FESC, FSCAI) College of Medicine -university of Kufa
Akeel AMH Zwain College of Medicine -university of Kufa
Amina A Al-Dijaili College of Medicine -university of Kufa
Correspondence to drzwain@zwayn.com

الخلاصة

خلفية البحث :أن مؤشر أجهاد البطين الأيسر الانقباضي للألياف الطولية (LVMESS) يعتبر عاملا أساسيا في تقييم أداء البطين الأيسر. هنالك عوامل رئيسية تؤثر على LVMESS ،منها سمك جدار البطين الأيسر و حجم البطين وتكوين البطين التي من الممكن وجودها في كلا من السمنة و مرض السكري النوع الثاني . توجد تقارير كثيرة تؤكد تأثير عامل النمو الذي يشبه الأنسولين (1- IGF)على زيادة مؤشر كتلة البطين الأيسر (LVMI) ،وكذلك على ومستويات A1C .

الهدف : لاستكشاف ما إذا كان الارتباط القائم بين LVMESS و IGF -1 في البلازما ذات مغزى معنوي ، في الأفراد ذي الفئة العمرية المتوسطة و كبار السن الذين يعانون من السمنة المفرطة مع أو بدون النوع الثاني لداء السكري.

المنهجية : في هذه الدراسة المقطعية التي أجريت في مركز القلب المفتوح في محافظة النجف الأشرف تم فحص مجموعه تتألف من 145 مشاركا. أجريت مقارنة البدناء للفئة العمرية المتوسطة و كبار السن مع نفس الفئة العمرية للأشخاص مع أو بدون النوع الثاني لداء السكري . وتمت مقارنة LVMESS و IGF -1 بين الجماعات ؛ وقد تم تحليل الاختلافات بين المجموعات باستخدام المفردة الاختبار الخطي و اختبار الارتباط. وأعرب عن البيانات كما يعني ± SD، باستخدام SPSS في الإصدار 18 .

النتائج : أظهرت القيم انخفاض LVMESS بصورة ملحوظة في مرضى السكري . كانت مستويات تركيز IGF-1 أقل في مرضى السكري الذين يعانون من السمنة المفرطة و المسنين بدرجة معنوية كبيرة (ص = 0.462 ، 0.04 = P) .هنالك علاقة سلبية بين1-IGF و LVMESS في البدناء الأصحاء وكبار السن غير البدناء المصابين بداء السكري .

الاستنتاج : علاقة غير خطية بين مستويات تركيز IGF -1 و LVMESS تم الحصول عليها . يمكن الافتراض أنه بسبب علاقته السلبية مع LVMESS في كبار السن البدناء المصابين بداء السكري .

التوصيات: من الممكن استخدام مستويات IGF -1 لتكون بمثابة مؤشر لضعف وظيفة البطين الأيسر الانقباضية. بالإضافة إلى انه من الممكن إلقاء بعض الضوء على العلاقة IGF -1- LVMESS ، عند النظر في العلاج باستخدام IGF -1 للمسنين في ظروف معينة. كذلك نوصي باستخدام عينات اكبر حجما في بحوث أخرى لدراسة العلاقة المذكورة آنفا.

Abstract:

Background: Left ventricular meridional end systolic stress (LVMESS) is a quantitative determinant index of LV afterload which is an essential determinant of LV performance. The key factors influencing LVMSS, notably ventricular wall thickness, chamber size and configuration are shown to be altered by both obesity and type2 diabetes mellitus (T2DM). There exist reports implicating high free insulin-like growth factor 1 (IGF-1) but not growth hormone (GH) levels, with increased left ventricular mass index (LVMI), abnormal LV geometric remodelling, and A1c levels.

Objective: to explore whether a meaningful link exists between LVMESS and free IGF-1 plasma levels, in obese middle-aged and elderly individuals with or without T2DM.

Subjects and methods: In this cross sectional study, a total of 145 participants Involved. Middle aged and elderly obese individuals with or without T2 DM were matched with healthy lean subjects of the same age group, with or without T2 DM. LVMESS and IGF-1 levels were compared between groups; group differences were analyzed using unpaired t test and linear correlation test. Data were expressed as the mean ± S.D, using SPSS version 18).

Results: LVMESS values showed significant decrease in diabetic patients compared to control in both middle and old aged subjects. IGF-1, concentration levels were lower in the elderly obese diabetics compared to control, with significant (r=0.462; p= 0.04) negative correlation with LVMESS in healthy obese old aged, and a negative but non-significant correlation with LVMESS in lean old aged with or without diabetics.

Conclusion: Nonlinear correlation of IGF-1 levels with LVMESS obtained. It could   be hypothesized that because of its negative significant correlation with LVMESS in the elderly non diabetic obese, IGF-1 free level could be utilized to serve as a predictor of impaired LV systolic function in these subjects. In addition the results could shed some light on IGF-1- LVMESS relationship, when considering IGF-1 therapy in certain conditions.

Recommendation: It is suggested that using IGF-1 plasma levels in the elderly with or without T2DM could aid as predictor for LV global systolic dysfunction .However, larger sample size are to be considered.

Keywords: IGF- 1, left ventricular meridional end systolic stress, obesity, Type 2 Diabetes Mellitus.

INTRODUCTION:

Because of the biased validity of LV systolic function assessment by ejection fraction (EF) index, two other types of load independent estimates have been proposed for this purpose: the meridional LV wall stress which reflects the function of the longitudinal endocardial and epicardial fibers of the LV wall, has been used as an indirect measure of LV after load. The circumferential LV wall stress which is in line with the direction of the mid wall circumferential fibers and has been used as a measure of myocardial contractility [1,2] . The concept of after load literally means the stress encountered by LV myofibrils as they contract against the end-diastolic volume/ intra -ventricular pressure. obese individuals with or without diabetes tend to develop left ventricular (LV) structural changes in response to the operating overload: volume overload causing chamber dilation in proportion to mass (eccentric hypertrophy), and pressure overload   producing increased LV mass out proportion to volume (concentric hypertrophy).   These patterns of hypertrophy are independent of arterial pressure and age [3, 4].

Diabetic and hypertensive subjects have a higher likelihood to develop, impaired diastolic function, in addition to decreased afterload measured by meridional end-systolic stress, as compared with lean individual [5,6]. Indeed, DM exclusively, can elicit changes in cardiac structure and function which are independent of associated ischemic heart disease or hypertension or increased BMI [7,8]

Mounting evidence indicate growth hormone (GH)/ Insulin growth factor 1(IGF-1) axis also known to contribute to LV structural and functional modulations: Circulating IGF-1 is synthesized primarily by the liver under the control of growth hormone (GH) [9]. However, IGF-1 can be synthesized by many other organs, including heart, and can act as an autocrine or a paracrine factor [10]. IGF-1 circulates bound to protein carriers (IGFBPs), which serve not only to transport IGF-1 in the circulation but also to prolong its half-life, modulate its tissue specificity and strengthen or neutralize its biological actions [11]

As growth factors, both GH andIGF-1 modulate myocyte growth and hypertrophy in the developing heart. IGF-1 has been demonstrated to induce nitric oxide (NO) production in vitro and has vasodilatory properties consistent with an NO-mediated effect in vivo that induces cellular proliferation and differentiation. In addition, it exerts both inotropic and growth effects that can influence LV geometry ([12,13]. However, until the time of preparation of this manuscript, studies on the impact of alteration of IGF-1 axis on meridional LV wall stress in obesity and obesity- related T2DM, are lacking.

Objectives

This study defined whether a relationship exsist between LVMESS and free LGF-1 plasma levels in obese middle age and elderly individuals with or without T2DM.

METHODOLOGY

A total of 145 participants were recruited from Al Najaf cardiac center, after having their verbal and written consent and approval from the ethical committee at our hospital. The subjects were classified into 3 groups. Group 1 subjects served as a control and were subdivided into group 1A, comprised healthy lean middle-aged (n=18, mean age 53 ± 4.3yrs, and BMI 23 ± 2.8 kg/ m^2), and healthy lean old aged individuals (n=15; mean age 64 ± 3.2; BMI 24 ± 1.7 kg/ m^2). Group 1B, involved diabetic lean middle-aged (n= 14; mean age, 57 ± 3.8yrs; BMI 22.4 ± 3.23 kg/ m^2), and diabetic lean old-aged (n= 21; mean age, 60 ± 3.3yrs; BMI, 21.5 ± 4.3 kg/ m^2). Group 2 involved healthy obese middle-aged (n=17; mean age, 48 ± 36 yrs; BM, $I34.5\pm7.6$ kg/m^2), and old aged obese subjects(n=29; mean age 65 ± 5.3 yrs; BMI, 32.5 ± 4.3 kg/m^2), and group 4, involved diabetic obese middle-aged (n=15; mean age,57 ± 3.8yrs; BMI 30.4 ± 6.23 kg/m^2), and diabetic old-aged subjects (n=16; mean age, 64 ± 2.8yrs; BMI, 32.5 ± 4.3 kg/ m^2). The inclusion criteria in this study were the exclusion of hypertension by an extensive examination, absence of cardiac or other chronic diseases, no metabolic disorders or pregnancy among women and good-quality echocardiograms at baseline evaluation. No subject was a competitive athletics. History should be taken to rule out medication intake, smoking habit, number of cigarette, duration of diabetes regarding diabetics' patients. The volunteers and patients had their body weight measured by using weight device with subject wearing no shoes. Height was measured by using a tape measure. Body mass index (BMI) was calculated as weight divided by height (kg/ m^2) according to the universal formula[14].

Left ventricular end systolic stress (LVMESS) can be calculated from the LV peak pressure P, the myocardial area "Am", and the LV cavity area "Ac" in the short-axis view at the papillary muscle level done at end-systole.

LVESMS = 1.33P (Ac/Am) x 103 dyne/cm³. (Reported normal values for LVESMS between 65 to 73 dynes/ cm³ [15].

Echocardiography

All patients had a resting echocardiography with commercially available tranthoracic echocardiography (Philips HDI 22100/ IE33, Bothell, A 98021-8431 made in USA) in cardiac center in AL Sader Teaching hospital, with the patients in partial left decubitus position. Two-dimensional and M-mode echocardiography are utilized to assess end-systolic meridional stress and its relationship to left ventricular cavity length, end-systolic circumferential stress and its relationship with left ventricular internal diameter.
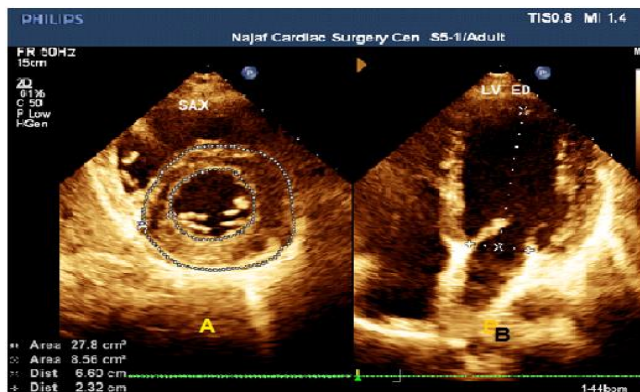

Fig 1 (A) Short-axis view of the left ventricle, at end-systole. (B) Apical four chamber view to assess LV diastolic length.

Laboratory assay

Fasting blood samples for at least 12 hrs were collected according to a standardized protocol from each subject; 6 ml of blood was drawn. Filled syringes were kept at 5-10 c, protected from light, and transferred to a local laboratory for centrifugation. 3 serum tubes for each sample were collected and freeze at -20°c until the time of assay.

Human IGF-1 was used (IGF-1 600 ELISA was manufactured by Demeditec Diagnostic GmbH.Lise-Meiter-StraBe2.D-24145 Kiel, (Germany). ELISA technique for direct quantitative determination of human IGF-1 levels

Statistical Analyses

Data were analyzed as per age groups group I (20-40 yrs), group II (40-60 yrs), group III (60-80yrs); each age group was further divided into 3 groups according their BMI into lean those has BMI < 25 kg/m2; overweight, those with BMI ranging from 24.9-29.9 kg/m2 and obese those with BMI > 30 kg/m2 .The results were expressed as mean and standard deviations. Analysis of variance (ANOVA) as well as correlation regression test and independent T test (using SPSS version 18) were applied to compare the study groups. Probability P value of < 0.05 was considered statistically significant ($\alpha \leq 0.05$)

RESULTS

Table 1: Subjects' profile of echocardiographic and IGF-1 levels in healthy individuals and diabetics, of age ranging between 40-60 yrs (n=64)

Groups		LVESMS dyne/cm	LVMI	LVM	IGF-1ng/ml
Lean	Diabetic n=14	49.88±22.82	174.13±52.57	182.03±49.15	44.67±19.77
	Healthy n=18	66.27±25.53	204.20±38.37	219.04±69.5	49.89±23.18
	P value	0.084	0.05	0.40	0.561
Obese	Diabetic n= 15	53.13±19.92	157.21±55.11	212.2±52.27	47.50±23.18
	Healthy n=17	62.52±11.93	200.42±100.16	245.5±45.82	48.05±35.78
	P value	0.05*	0.141	0.12	0.959

Table 1 shows that, in lean middle- aged individuals, LVMESS did not show a statically significant difference between diabetics and healthy individuals. Whereas in obese middle- aged individuals, a significant decrease in LVMESS in diabetics was observed compared to healthy individuals. The LVMI showed a decrease in obese individuals in both diabetics and healthy subjects, but this decrease did not reach a significant level. LVM showed a significant increase in obese subjects in both diabetics and healthy individuals, but this increase did not reach a significant levels. In this age group, in diabetics and healthy individuals, the IGF-1 circulating levels, showed no significant differences among different BMIs.

Table 2: Difference values of LVM in lean and obese healthy and diabetic subjects

LVM	P value
Lean healthy middle age subjects n=18	0.04
Obese healthy middle age subjects n=17	
Lean diabetic middle age subjects n=14	0.5
Obese diabetic middle age subjects n=15	

Table 2 shows that regarding LVM, There are a significant differences between lean and obese healthy middle age individuals (p=0.04), whereas no significant difference between lean and obese diabetic subject in the same age group (p=0.5)

Table 3: Subjects' profile of echocardiographic data and GH/IGF-1 levels in healthy individuals and diabetics of age >60yrs, of different BMIs.n=81

groups		LVESMS dyne/cm	LVMI	LVM	IGF-1ng/ml
Lean	Diabetic n=21	44.86±12.36	127.88±69.89	167.7±75.4	20.24±22.10
	Healthy n=15	51.88±9.69	141.33±87.00	179.61±83.61	40.46±6.54
	P value	0.151	0.943	0.99	0.008**
Obese	Diabetic n=16	51.05±23.19	149.84±39.16	129.02±80.01	17.68±5.39
	Healthy n=29	54.20±12.66	167.87±89.62	134.08±112.63	19.68±7.43
	P value	0.724	0.341	0.50	0.281

Table 3 shows that the elderly (>60yrs), in both diabetics and healthy individuals, the LVMESS did not show statistical significant variation at different BMIs, in both diabetics and healthy subjects. The LVMI did not show statically significant changes in different BMIs in both diabetics and healthy individuals. In this group, the GH did not show significant variation between diabetics and healthy individuals. The IGF-1 showed significant increase in diabetics, only in lean subjects (p < 0.01). No statistical significant changes in IGF-1 observed in obese subjects,. Independent sample t-test, ** significant at (P≤0.05)

Table 4: difference values of LVM in lean and obese healthy and diabetic subjects.

LVM	P value
Lean healthy old age subjects n=15	0.06
Obese healthy old age subjects n=29	
Lean diabetic old age subjects n=21	0.7
Obese diabetic old age subjects n=16	

Table 4 shows that in both healthy and diabetic individuals there are no significant difference in LVM between lean and obese subjects.(p=0.06;0.7 respectively).
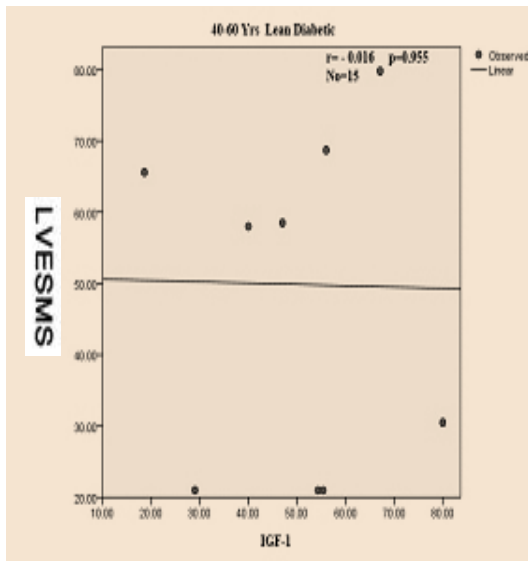
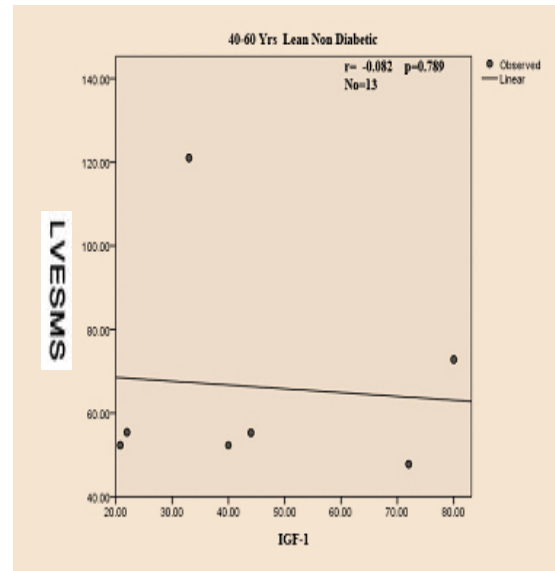Figure 1.a correlation of LVESMS with IGF-1in lean diabetics, 40-60 yrs

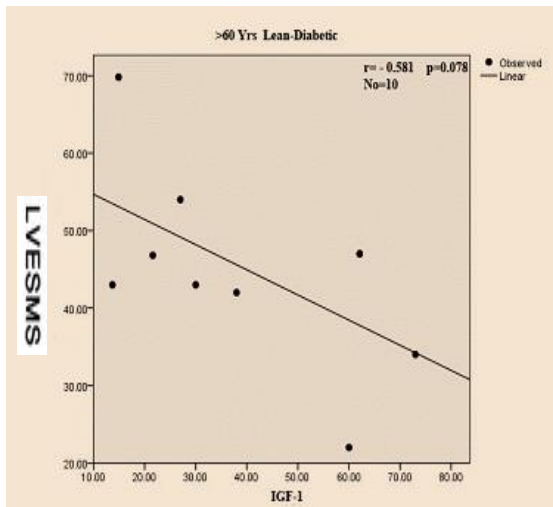Figure 1.b correlation of LVESMS&IGF-1 in lean healthy, aged aged 40-60 yrs

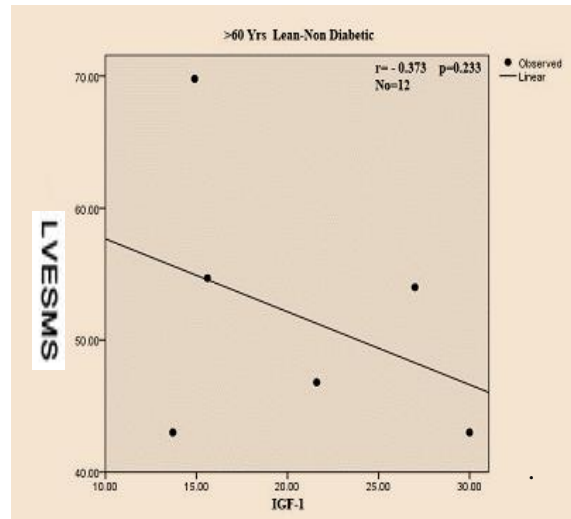Figure 2.a correlation of LVESMS & IGF-1in lean diabetics aged >60 yr

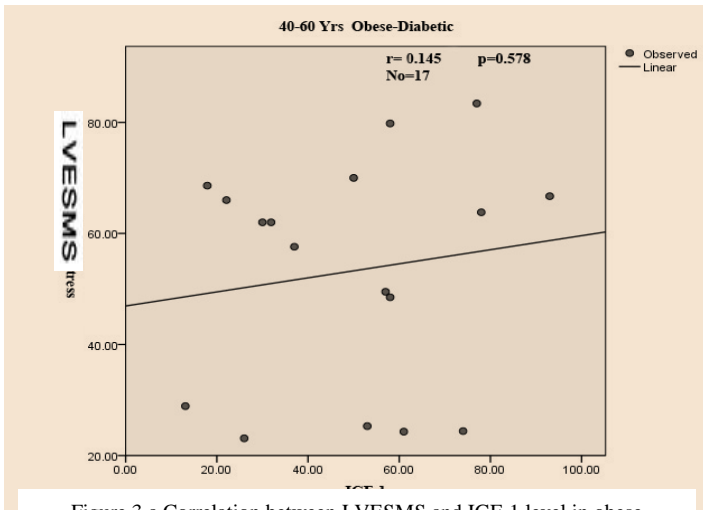Figure 2.b correlation of LVESMS&IGF-1 in lean healthy aged >60 yrs

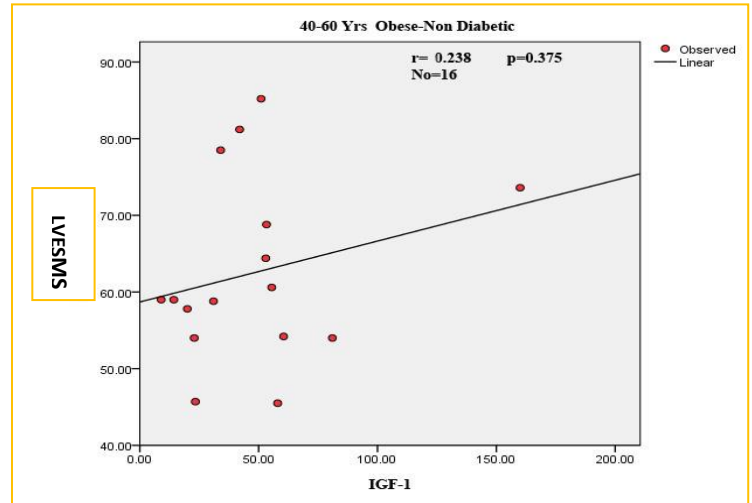Figure 3.a Correlation between LVESMS and IGF-1 level in obese diabetics aged 40-60 yrs.

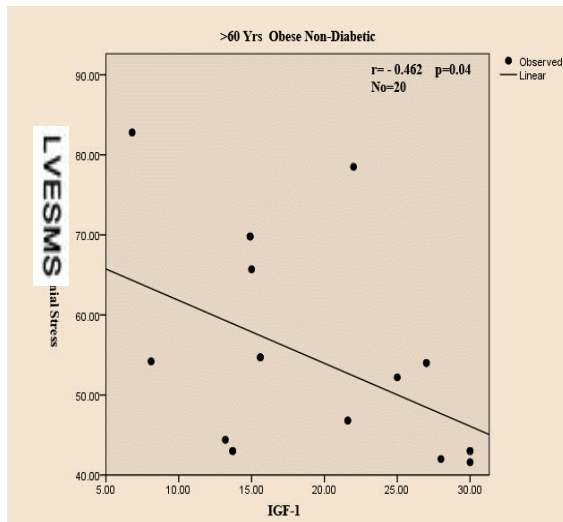Figure 3.b Correlation between LVESMS and IGF-1 level in obese non diabetics aged 40-60yrs.

Figure 4.a correlation between LVESMS and IGF-1 in lean diabetics >60 yrs
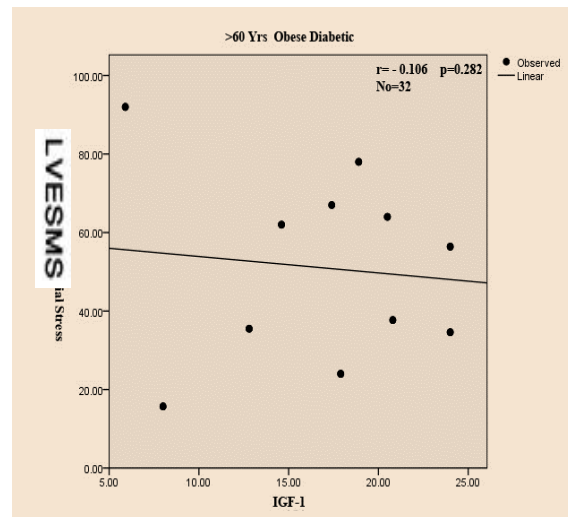

Figure 4.b correlation between LVESMS and IGF-1 in aged lean healthy, aged >60yrs

In middle age healthy lean individuals (age 40-60 yrs, n=13, BMI<25 kg/m^2), the mean values for LVESMS, IGF-1 plasma levels were 71.74 ± 13.50 dynes /cm^3 and 38.31±10.65ng/ml, respectively. In this group, IGF-1 had no significant correlation with the LVESMS, p value 0.7, r = 0.08. In middle- aged obese healthy individuals (age 40-60 yrs, n=16, BMI<25 kg/ m^2), the mean values for LVESMS and IGF-1 plasma levels were 61.23 ± 20.11dyne/cm^3 and 37.58± 30.22 ng/ml respectively. No significant correlation was observed between IGF-1 levels and LVESMS, (p value 0.37, r =0.23), as shown in figures 1b and 3b.

In the elderly lean healthy individuals (age>60 yrs, n=12, BMI>25), the mean values of LVESMS; GH, IGF-1 plasma levels were 60.4±14.3dyne/cm^3; 1.617 ± 0.88 ng/ml ;49.22±34.980 ng/ml, respectively; a negative non-significant correlation was observed between IGF-1 and

LVESMS, p =0.23, r=0.37. Whereas In the elderly obese healthy individuals(age>60 yrs, n=20, BMI >) the mean values of LVESMS; GH, IGF-1 plasma levels were 58.4±14.3dyne/cm ^{3}; 1.421 ± 0.78 ng/ml ; 44.22±32.970 ng/ml, respectively; a negative significant correlation was observed between IGF-1 and LVESMS, p =0.04,r=0.46, as shown in figures 2a and 4a

In middle-aged lean diabetics, (n=15), the mean±S.D values for LVESMS and IGF-1, levels were 53.9± 17.8 dynes/cm^3 and 44.54 ng/ml, respectively. There was no significant correlation observed between IGF-1 level and LVESMS, (p=0.95; r=0.01). Whereas, in obese diabetics of age 40-60yrs, n=17,   the mean±S.D values for for LVESMS and, IGF-1, levels were 53.9± 17.8 dynes/cm^3 and 44.54 ng/ml, respectively There was a negative, but non-significant correlation observed between LVESMS and IGF-1 level (p=0.57, r=0.14),as shown in figures 1a and 3a.

In the elderly lean diabetics (n=10), the mean values of LVESMS andIGF-1, levels were 49.7± 17.8 dynes/cm^3 and 39.44 ng/ml, respectively. There was a negative non-significant correlation observed between LVESMS and IGF-1 level (p=0.07;r=0.58). Whereas in the elderly obese diabetics (n=32), the mean values of LVESMS and IGF-1, levels were 48.4± 15.8 dynes/cm ^{3} 0.43 ±1.90 ng/ml and 37.8 ng/ml, respectively; no significant correlation observed between LVESMS and IGF-1 level (p=0.28;r=0.10), as illustrated in figures .a and 4b.

Regarding correlation of LVM with IGF-1, in both middle and old age show no significant correlation except in elderly obese diabetic subjects show negative significant correlation (p=.0001).

DISCUSSION

In certain progressive metabolic disorders, such as obesity, and obesity related T2DM, the impact of alteration in the circulatory IGF-1 levels, on overall myocardial performance has featured the interest of several studies.

The present results showed increased LVM in obese individuals with or without diabetes , these results are consistent with the previous studies demonstrating both obesity and type 2 diabetes could cause abnormalities in cardiac geometry (remodeling) and function independent of coronary artery ischemia and hypertension [16, 17] . Hence, according to laplace's law, the LVMSS decreased in these patient (tables 3 and 4). Our data contradict with study of Postel-Vinay et al.[18] . Their conclusion was that increased systolic function measured by increased shortening fraction and lower wall stress could occur in obese young adult. The discrepancy of the results may be attributed to the differences in the measures used for estimation of LV systolic function.

In the present study, age related to IGF-1 levels were demonstrated. IGF-1 levels relatively increased in middle aged and decreased in the elderly obese individuals. No significant correlations were found between IGF-1 and BMI or other indices of adiposity. These results corroborates with the past investigations [19].

Regarding the proposed link between LV mass and free IGF-1 circulating levels, our data showed   a multifaceted interrelationship which was also in agreement with other researchers. A negative correlation between IGF-1 and LVM observed in the lean and obese elderly, with or without diabetes. Whereas a positive correlation observed in lean and obese middle aged with or without diabetes [20]. Owing to its load independency, we implemented the use LV meridional stress as a parameter of LV Afterload measure to reflect LV systolic function taking into account the closely inter-related factors that are known to influence LV systolic function notably, the BMI, LV

ventricular mass and and GH/IGF-1 axis. Of note, the reported normal IGF-1 plasma levels by several investigators are wide raged and conflicting. This inconsistency was attributed to differences in age, sex and the degree of obesity [20]. In an attempt to study the free GH/IGF-1 levels in middle- aged Korean obese males, Maccaario etal [21] showed in obese individuals, The GH level was reduced, whereas IGF 1 level did not differ significantly. However, the author reported that inconsistent results presented by others due to differences in age, sex and the degree of obesity.

In this study, non- linear relationship existed between IGF-1 levels and LVMSS in age adjusted obese groups. Non significant relationship in the young, significant inverse relationship in the middle aged diabetics and negative but non significant association in the elderly healthy obese. A wide range of mechanisms involving interactions among several factors. The inconsistency of these findings could be explained by the following : 1) IGF-1 bioactivity is more in young and middle aged, a decreased bioavailabiliy in the elderly [21, 22], 2) GH/IGF-1 deficiency contributes to physiological age-related cardiovascular modifications, such as decrease in the number of cardio myocytes [22], 3) a wide range of IGF-1 normal plasma levels have been reported by considerable number of literature, 4) a possible IGF-I /leptin interplay: it has been shown an inverse association between leptin and IGF1, 5) in the obese, there could be an interplay between leptin, GH-IGF-1 axis and insulin resistance. In the obese, it has been shown that GH/IGF-1 axis can be altered at different levels, And finally, The GH secretion is blunted GH secretion may be paired with either normal, low or high IGF-1 levels. IGF-binding protein-1 (IGFBP-1) and IGFBP-2 plasma levels are blunted due to inhibition by insulin, which is generally increased in obese subjects [22, 23].

It is pertinent to point out that total IGF-1 concentrations do not necessarily reflect IGF- 1 activity. Recently, the IGF-1/IGFBP-3 molar ratio has been indicated to reflect the amount of unbound and biologically active IGF-1 [23]. However, a low level in old age may indicate impaired LV function, though this notion necessitates large sample studies.

CONCLUSION

IGF-1 level– LVMESS relationship can be modulated by age, obesity and obesity related diabetes. The inverse association of IGF-1 level with LVMESS in middle aged diabetics and elderly healthy obese subjects may raise the speculation of its utility as a predictor for assessment of LV systolic function.

RECOMMENDATION

It is suggested that using IGF-1 plasma levels in the elderly with or without T2DM could aid as predictor for LV global systolic dysfunction .However, larger sample size are to be considered.

REFERENCES

1. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, WeltyTK, et al. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation 2000; 101:2271-6.
2. Vittorio Palmieri , Cesare Russoa, Emma Arezzi , Salvatore Pezzullo ,Maria Sabatella , Stefana Minichiello , Aldo Celentano . Relations of longitudinal left ventricular systolicfunction to left ventricular mass, load, and Doppler stroke volume. Eur J Echocardiography (2006) 7, 348e355.
3. C.J. Lavie, R.V. Milani, H.O. Ventura, G.A. Cardenas, M.R. Mehra, F.H. Messerli. Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction. Am J Cardiol, 100 (2007), pp. 1460–146]

4. A. S. Shah & P. R. Khoury & L. M. Dolan & H. M. Ippisch & E. M. Urbina & S. R. Daniels & T. R. Kimball. The effects of obesity and type 2 diabetes mellitus on cardiac structure and function in adolescents and young adults. Diabetologia (2011) 54:722–730.

5. Jeong-Hwan Park, Il-Suk Sohn*, Jin-Man Cho and Chong-Jin Kim. Impact of Diabetes on the Left Ventricular Long Axis and Midwall Function in Patients with Hypertension. Chonnam Medical Journal 2009 Vol. 45, No. 1, pp. 27~32

6. Carl J. Lavie, MD Richard V. Milani, MD, Hector O. Ventura, MD. Obesity and Cardiovascular Disease: Risk Factor, Paradox, and Impact of Weight Loss. Journal of the American College of Cardiology. Volume 53, Issue 21, 26 May 2009, Pages 1925–1932.

7. Richard B. Devereux, MD; Mary J. Roman, MD; Mary Paranicas, BA; Michael J. O'Grady, BA; Elisa T. Lee, PhD; Thomas K. Welty, MD, of Diabetes on Cardiac Structure and Function. The Strong Heart Study. Circulation. 2000; 101: 2271-2276 .

8. Fazio S, Palmieri EA, Biondi B, Cittadini A, Saccà L. The role of the GH-IGF-1 axis in the regulation of myocardial growth: from experimental model to human evidence. Eur J Endocrinol. 2000;142:211–6. [PubMed]Tsukahara H, Gordienko DV, Tonshoff B, et al. Direct demonstration of insulin like growth factor I induced nitric oxide production by endothelial cells. *Kidney Int.* 1994;45:598–604.

9 Fryburg DA. Nc-Monomethyl-l-arginine inhibits the blood flow but not the insulin like response of forearm muscle to IGF-1: possible role of nitric oxide in muscle protein synthesis. J Clin Invest.. 1996;97:1319–1328..

10 Reiss K, Kajstura J, Capasso JM, Marino TA, Anversa P. Impairment of myocyte contractility following coronary artery narrowing is associated with activation of the myocyte IGF-1 autocrine system, enhanced expression of late growth related genes, DNA synthesis, and myocyte nuclear mitotic division in rats. Exp Cell Res. 1993; 207: 348–360.

11 Cittadini A, Stromer H, Katz SE, Clark R, Moses AC, Morgan JP, Douglas PS. Differential cardiac effects of growth hormone and insulin-like growth factor-1 in the rat: a combined in vivo and in vitro evaluation. Circulation. 1996; 93: 800–809.

12 Kumar S, Khunti K, Wasim H, Zaman J . Position Statement on Diagnosis and Treatment of Obesity in British South Asians. London: South Asian Health Foundation *2010.*

13 A. S. Shah & P. R. Khoury & L. M. Dolan & H. M. Ippisch & E. M. Urbina & S. R. Daniels & T. R. Kimball. The effects of obesity and type 2 diabetes mellitus on cardiac structure and function in adolescents and young adults]. Diabetologia (2011) 54:722–730

14 Gómez JM, Maravall FJ, Gómez N, Navarro MA, Casamitjana R, Soler J. Interactions between serum leptin, the insulin-like growth factor-I system, and sex, age, anthropometric and body composition variables in a healthy population randomly selected. Clin Endocrinol (Oxf). 2003 Feb;58(2):213-9.

15 Olivetti G, Melissari M, Capasso JM, Anversa P. Cardi omyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circ Res. 1991;68:1560–8. [PubMed

16 Scacchi M, Pincelli AI, Cavagnini F 1999 Growth hormone in obesity. Int J Obes Relat Metab Disord 23:260–271

17 Postel-Vinay MC, Saab C, Gourmelen M1995 Nutritional status and growth hormone-binding protein. Horm Res.44:177–181.

18 Nam SY, Lee EJ, Kim KR, Cha BS, Song YD, lim SK, et al. Effect of obesity on total and free insulin-like growth factor (IGF-1), and their ralationship to IGF-binding protein (BP)-1,IGFBP-2, IGFBP-3, in-sulin, and growth hormone. Metabolism 2001; 56: 292-6.

19 Juul A, Dalgaard P, Blum WF, Bang P, Hall K, Michaelsen KF, et al. Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the

relation to IGF-1, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. J Clin Endocrinol Metab1995; 80: 2534-42.

20 Maccaario M, Ramunni J, Oleandri SE, Procopio M, Grottoli S, Rossetto R, et al. Relationships be-tween IGF-1 and age, gender, body mass, fat dis-tribution, metabolic and hormonal variables in obese patients. Int J obes Relat Metab Disord 1999; 23: 612-18.

21 Michael Højby Rasmussen, Jan Frystyk, Teis Andersen , Leif Breum, Jens Sandahl Christiansen, Jannik Hilsted. The impact of obesity, fat distribution, and energy restriction on insulin-like growth factor-1 (IGF-1), IGF-binding protein-3, insulin, and growth hormone. Metabolism, Volume 43, Issue 3, March 1994, Pages 315–319

22 Norstedt G, Palmiter RD.Regulation of insulin-Like growth factor 1gene expression by growth hormone.Proc Natl Acad USA.1996;83;9343-9347.