Arab J. Nucl. Sci. Appl., Vol. 56, 1, 146-152 (2023)

ISSN 1110-0451

Arab Journal of Nuclear Sciences and Applications

Web site: ajnsa.journals.ekb.eg

(E S N S A)

Assessment of Framingham Risk Score and Serum Leptin in Patients with Skin Tag

Ghada K. El Khalafawy, Eman M. Elgazzar and Eman S. Eldin*

Health Radiation Research Department, National Center for Radiation Research and Technology, Egyptian Atomic Energy authority, Cairo, Egypt

ARTICLE INFO

Article history:

Received: 20th June 2022

Accepted: 11th Sept. 2022

Keywords:

Skin tag,
leptin,
Framingham risk score

ABSTRACT

Skin tags are common dermatological lesions that have been linked to metabolic syndrome, which includes diabetes, obesity, and hypertension, as well as cardiovascular disease. Increased adipose deposition and serum leptin levels may be associated with skin tags (STs). The relationship between serum lipid profile and serum leptin levels in patients with skin tags and the Framingham risk score was investigated. The Framingham risk score (FRS) is a method to calculate the likelihood of getting cardiovascular disease (CVD) during a 10-year period (CVD). The current study was carried out on 60 participants; 30 patients with STs and 30 apparently healthy as controls. Serum lipid profile and serum leptin were measured. There was Statistically significant difference of serum leptin level between skin tag (22.6±16.4 ng/ml) group and control (13.23±10.14 ng/ml) and cholesterol also showing significant difference between skin tag disease group (183.3±37.12 mg/dl) and the control group (155.6±21.86 mg/dl). Other parameters Low Density Lipoprotein (LDL), Triglycerides (TG) and non-High-Density Lipoprotein, cholesterol (non-HDL) show no significant difference between the two groups. An assessment was performed to differentiate between skin tag and Framingham risk score. It was found that 70% of patients are in high and moderate risk group. The present study found association between skin tag patients and Framingham risk score.

INTRODUCTION

Skin tags are prevalent lesions that are formed of loose fibrous tissue and usually appear on the neck and major flexures. They usually take the form of small, soft, pedunculated protrusions [1].

Skin tags can appear at any age and are equally prevalent in both men and women [2], the cause of a skin tag is uncertain [3]. Several variables have been linked to skin tags, including familial history, pregnancy, impaired glucose metabolism, obesity, and friction. Metabolic syndrome may be linked to skin tags [4, 5].

Leptin is a hormone that is derived from adipocyte that controls food intake, energy expenditure, and body weight by acting on the hypothalamus. It is formed by the ob (obesity) gene and exerts biological effects via the leptin receptor (ob-R) [3, 5]. It is a 167-amino-acid protein with a molecular weight of 16 kDa which modulates appetite and energy expenditure [5, 6]. Skin tags are usually related with obesity and higher serum leptin levels in obese people. The activation of leptin receptors in the dermis and epidermis causes keratinocytes and fibroblasts to differentiate and proliferate, resulting in the formation of skin tags [2, 6].

The FRS method is a simplistic and frequently used method for estimating the risk of heart disease over a 10-year period [7]. The FRS includes age, gender, total cholesterol, high density lipoprotein cholesterol, smoking behaviors, and systolic blood pressure as six coronary

Corresponding author: emanserag1979@yahoo.com
DOI: 10.21608/ajnsa.2022.145911.1605

risk factors [8]. The FRS is the most applicable approach for estimating a person's long-term risk of cardiovascular disease [9]. This risk score can be useful for patients and clinicians when assessing whether lifestyle changes and prophylactic medical therapy are necessary, as well as health education by detecting men and women who are at higher risk for the development cardiovascular events [10].

The Framingham risk score is the easy method to predict cardiovascular diseases in metabolic disorders using skin tag as a landmark.

SUBJECTS AND METHODS

The participants of the study were subdivided into 30 patients seeking advice for their STs and 30 seemingly healthy volunteers who served as controls. They attended to Mustafa Mahmoud Hospital's dermatology clinic. Each subject of the study had signed an informed consent. The inclusion criteria focused on patients of age 30 – 60 years old with skin tag at any location who agree to participate in the study. Exclusion criteria were pregnant, lactating women, chronic renal insufficiency and liver diseases.

A specially created questionnaire was developed to collect individual data such as age, sex, occupation, history of diabetes, history of cardiovascular disease, history of hypertension, evolution of skin tag onset, number, site, size, type, and color of skin tags.

Height, body weight, and waist measurement had been measured, and the body mass index (BMI) was calculated by dividing the kilograms by the square of the height in meters. BMI 25-30 kg/m^2 was considered overweight, whereas BMI >30 kg/m^2 was considered obese [10].

At the enrollment visit, venous blood samples were collected after subjects had fasted overnight. The serum had been collected, divided into aliquots, and kept at -20°C until analysis. An enzymatic approach was utilized to determine serum total cholesterol and total triglycerides using commercial kits (Bio diagnostics, USA). Phosphotungstate precipitation of serum high density lipoprotein (HDL), followed by an enzymatic technique Friedewald's formula was used to calculate serum low density lipoprotein (LDL) cholesterol and non-HDL cholesterol. A completely automated analyzer was used to analyze all of the parameters.

The level of leptin in the blood was measured using an enzyme linked immunosorbent assay (ELISA) (diagnostic Biochem canda,USA, CAN-L4260,Lot 202150).

Framingham risk score (FRS)

The FRS system has been created to look at the risk of heart disease over the course of ten years. FRS scores were calculated using age, sex, TC, HDL-cholesterol, systolic blood pressure, smoking habits, diabetes, and CVD history. The following were the cutoffs for calculating FRS: 160, 160–199, 200–239, 240–279, and 280 mg/dL for TC; 120, 120–129, 130–139, 140–159, and 160 mmHg for systolic blood pressure; and 40, 40–49, 50–59, and 60 mg/dL for HDL. Low risk (less than 10%), intermediate risk (10–20%), and high risk (more than 20%) were assigned to the absolute CVD risk percentage over a 10-year period [8].

Statistical analysis

Using the computer application SPSS version 10 for Windows, data were statistically analyzed utilizing an unpaired Students t-test and an ANOVA test. The significance level was chosen at P 0.05.

RESULTS

The personal data of the skin tag individuals in the current study are shown (Table 1). These included sex, age, family history, and skin tag duration. The mean age group of skin tag is (48.97 ± 1.598) and the mean age control group (40.20 ± 1.465).

Multiple skin tags lesions were found in 25 patients (83.3%) and a single lesion in 5 patients (16.7%) (Table1), the skin tag onset was variable between the patients. The mixed form of skin tag lesion was found to be the most frequent (56.6 %) (Table 2). BMI showed statistical significance between study and control group with (p value= 0.025) (Table 1). In the present study 60% of the patients with skin tag have family history of skin tag and 16.6% of the patients have history of cardiovascular disease, 20% are diabetic patients and 33.3% of the patients have history of hypertension.

Table (1): Demographic data of the subjects

Variable	Cases	Controls
Number of subjects	**30**	**30**
Age	48.97 ± 1.598	40.20 ± 1.465
Male : female	18:12	13:17
Number of skin tags:	1-30	
solitary skin tag	16.7%	None
Multiple skin tags	83.3%	
Onset of skin tags	variable	None
Family history of skin tags	60%	None
Waist circumference	106.7±10.10	103.7±6.1
BMI	34.48±7.5*	29.3±1.7
Smoking	30%	24%
Family history of CVD	16.6%	None
History of HTN	33.3%	None
History of DM	20%	None

BMI=Body mass index (Kg/m^2), CVD=cardiovascular disease, DM= Diabetes Mellitus, HTN=hypertension.
*= statistical significance by t test

Table (2): Distribution of skin tag patients based on the type of lesion

Type of lesion	Percentage%
Mixed	56.6%
Pedunculated	33.3%
Non pedunculated	10%

In the present study, there is a significance difference between mean of leptin in disease group (22.6±16.4 ng/ml) and control group (13.23±10.14 ng/ml) with (P=0.027) (Figure.1) and also cholesterol and HDL showing a significant difference between the two groups as cholesterol mean in skin tag disease group (183.3±37.12 mg/dl) and the control group (155.6±21.86 mg/dl) while HDL mean in skin tag group is (40.4±8.8 mg/dl) and mean in the control group is (35.16±7.05 mg/dl) Other parameters such as LDL, TG and non-HDL show no significant difference between the two groups (Table 3).

Table (3): Comparison of lipid profile among the study groups

Parameters	Mean of Skin Tag group	Mean of control group	P value
Leptin(ng/dl)	22.6±16.4*	13.23±10.14	0.027
Cholesterol(mg/dl)	183.3±37.12*	155.6±21.86	0.025
LDL(mg/dl)	119.7±29.41	98.1323.39	ns
HDL(mg/dl)	40.4±8.8*	35.16±7.05	0.03
TG(mg/dl)	149±61.33	136.9±61.62	ns
Non HDL(mg/dl)	143.9±31.72	130.8±24.82	ns

TG = Triglycerides, HDL = High density Lipoprotein, LDL= Low density lipoprotein, non HDL=non High density Lipoprotein.
*= statistical significance by t test
P>0.05=no statistical difference was seen between cases and control group.

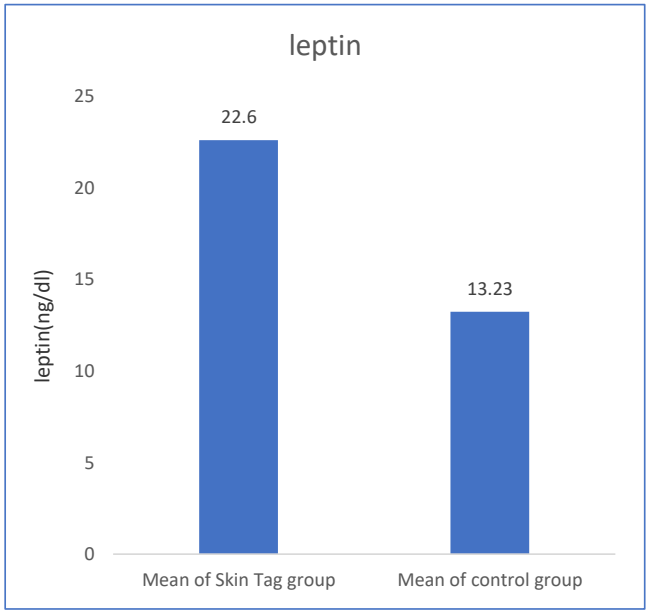

Fig. (1): A comparison of mean of leptin levels between skin tag group and the control group

Significant differences were noted between the low, moderate, and high-risk categories; the majority of skin tag patients (>20%) are in the high FRS risk category (43.3%), and all skin tag patients with hypertension, diabetes, and smokers are in the high and moderate risk groups (Table 4).

Table (4): Association between skin tag patients and Framingham risk score classification

Parameters	FRS > 20% High risk	FRS 10–20% Moderate risk	FRS <10% Low risk	P value
percentage	43.3%*	26.7%	30%	
Gender(M/F)	10/3	8/0	3/6	
Age mean	50.42±7.9*	54.25±6.6*	41.13±7.8	0.027[1] 0.004[2]
TC	170±10	181±13	193±46	NS
HDL	38±7.0	41±8.8	37±8.8	NS
SBP	137.5±23*	124±16	119±4	0.034[3]
Smoker	38.5%	37.5%	None	
DM	46%	None	None	
HTN	61.5%	25%	None	
History of CVD	30.7%	25%	None	

TC = Total Cholesterol, HDL = High density Lipoprotein & SBP = Systolic blood pressure, DM= Diabetes Mellitus, HTN=Hypertension, CVD=cardiovascular disease, NS= non-significant

1= significant difference between high and low risk group & 2= significant difference between moderate and low risk group & 3= significant difference between high and low risk group.

DISCUSSION

The most frequent fibrous lesions of the skin are skin tags [11]. Skin tags may be accompanied with some endocrine diseases and most of patients are not alert about that [12]. Obesity, diabetes, dyslipidemia, and hypertension are all risk factors for CVD [13].

The majority of skin tag patients in the current study (56.6 %) has mixed type skin tag lesions, while ***Jusuf et al.*** observed that the majority of skin tag lesions are mixed type (56.2 %) [2]. The majority of our skin tag patients had several lesions, according to a number of skin tags (83.3 %). These findings were obtained by ***Jusuf et al.*** who discovered that 28 individuals (87.5%) had multiple lesions [2].

Obesity is defined as a BMI greater than 30 kg/m^2 and is linked to a variety of health issues, including insulin resistance, hypertension, and cardiovascular disease. Obesity prevalence has almost doubled globally over the last several decades, resulting in several of the obesity-related pathological diseases and creating major health hazards in the future [14].

Interestingly, the level of serum leptin follows a rhythmic cycle, with a high level at night. Moreover, because leptin concentration is linked to the quantity of fat tissue and BMI, it is usually characterized by elevated leptin levels [15]. Furthermore, elevated serum leptin levels are associated with leptin receptor resistance, and these disorders are linked to obesity [16].

The skin tag group had a higher mean BMI (34.48±7.50 kg/m^2) than that of the control group (29.98 ± 2.35 kg/m^2), according to the findings of the current study. These findings are in line with those of ***Tosson et al.*** who found that the BMI of the skin tag group (32.8 ± 4.4 kg/m^2) was greater than that of the control group (28.5 ± 2.9 kg/m^2) [5]. Obesity is marked by an increase in the lipid accumulation in the adipocyte, particularly triglycerides [17].

The link between STs and several biochemical indicators related to obesity and leptin, as well as the relationship with the Framingham risk score, were investigated in the present study. It was found that the skin tag group has a higher mean of serum leptin levels (22.6±16.4 ng/ml), higher than that in the control group (13.23±10.14 ng/ml). As a result, a significant difference in leptin levels between the skin tag and the control group (p=0.027) was detected. This finding agrees with that of ***Nurhayati et al.*** who discovered a mean of 29.89 ± 13.34 ng/ml in skin tag patients, which is greater than that of the control group (22.53 ± 12.91 ng/ml) with (P=0.034) [18]. ***El Safoury et al.*** observed that the serum leptin level mean in the skin tag group was higher

than that in the control group with statistically significant results at the significance level of $p<0.001$ [19].

The increase of the serum leptin in skin tag disease can be explained in the light that skin tag is mostly associated with excess adipose tissue that leads to increasing the serum leptin concentration and impairing the activation of leptin receptors on fibroblast, endothelial cells and keratinocytes due to impaired activity of leptin of many intracellular signaling especially the kinase-signal transducer and activator of transcription (JAK/STAT) pathway showing cellular effects as the increase of proliferation, differentiation, migration, stabilization of skin disease and also the increase of keratinocytes and fibroblasts [20].

Obesity is associated with an increase of the lipid accumulation in the adipocyte, primarily triglycerides. In the current work, total cholesterol and HDL levels were statistically significant. Although LDL and TG levels were higher in ST patients, the difference was not statistically significant (Table 3). Previous researches have also found a link between the lipid profile and STs, but the individual lipid levels differ. According to an earlier study by ***Erdogan et al.*** people with STs have a substantial increase in the total cholesterol [21, 22].

Another study discovered a link between STs and triglycerides, low-density lipoprotein, and very-low-density lipoprotein cholesterol [3]. ***Idris et al.*** showed that the mean TC levels and the TC/HDL-cholesterol ratio were considerably higher in the cases than in the control group in an Indian study [6].

Increased total cholesterol induces fat layer deposition in the vessel as well as blood flow disruptions. Even blood flow obstruction and elevated blood pressure, particularly in coronary heart arteries, stimulate macrophage activity and the manufacture of inflammatory mediators, precipitating CVD [23,24].

FRS is approved by the National Cholesterol Education Program (Adult Treatment Panel III) and has been validated and used in several research works [25, 10]. This score predicts people's 10-year CVD risk [26]**.** Clinical and analytical measurements are included in this scoring history [27].

The current study, explains the association between skin tag and FRS score, the study showed 43.3% of patient are at high-risk group (>20%), moderate risk (10-20%) are 26.7% of skin tag patients. Thus 70% of skin tag patients showed risk more than 10%. The age of the patients showed a significance difference between high and moderate risk groups in contrast with low-risk group.***Yang et al.*** found that age was the best index for predicting CVD in the Jiangsu population in China, indicating that age does play an essential role in predicting the development of CVD using FRS [28].

Furthermore, in the present study, smokers were concentrated in the high and moderate risk groups of FRSs, raising the probability of CVD start in the next ten years. In skin tag patients, 38.5% of the high-risk group and 37.5% of the moderate risk group are smokers.

Diabetes increases the risk of complications from cardiovascular disease, particularly atherosclerotic vascular disease. CV events are the leading cause of death in diabetes individuals [29,30].

It was found in the present investigation that about 46% of skin tag patients of FRS high risk group are diabetics which means that diabetes with skin tag may be associated with CVD. In addition, high Systolic blood pressure patients are classified in the medium and high FRS groups as represented by 61.5% of the high-risk group and 25% of the medium group. According to ***Zhang et al.*** patients in the medium and high FRS groups were also more likely to be older, have a longer history of diabetes, and have higher blood pressure than those in the low FRS group [29]. Another study found that skin tags were more common in diabetic and hypertensive patients, and that they were linked to higher SBP and HbA1c levels [13].

CONCLUSIONS

An association was found between skin tag patients and Framingham risk score mainly based on age, history of hypertension and diabetes mellitus which is an alarm of developing CVD in long term. There is a correlation between skin tag and serum leptin level and abnormal serum lipid profile was found in almost all patients with skin tag.

REFERENCES

[1] Rook, A., & Burns, T. (2010). *Rook's textbook of dermatology*. 8th edition 2010, p 52.40. Chichester, West Sussex, UK: Wiley-Blackwell.

[2] Jusuf, N. K., Putra, I. B., & Kartayana, J. (2017). The correlation between body mass index with the occurrence of skin tag. Open Access Macedonian Journal of Medical Sciences, 5(3), 271.

[3] Wali, V., & Wali, V. V. (2016). Assessment of various biochemical parameters and BMI in

patients with skin tags. Journal of clinical and diagnostic research: JCDR, 10(1), BC09.

[4] Tamega, A. D. A., Aranha, A. M. P., Guiotoku, M. M., Miot, L. D. B., & Miot, H. A. (2010). Association between skin tags and insulin resistance. Anais brasileiros de dermatologia, 85, 25-31.

[5] Tosson, Z., Ibrahim, S. A., Kandil, A. H., & Husam, M. (2013). Relationship between skin tags, leptin hormone and metabolic disturbances. Egypt Dermatology Online Journal, 9(2), 1-12.

[6] Idris, S., & Sunitha, S. (2014). Assessment of BMI, serum leptin levels and lipid profile in patients with skin tags. Journal of clinical and diagnostic research: JCDR, 8(9), CC01.

[7] Wannamethee, S. G., Shaper, A. G., Lennon, L., & Morris, R. W. (2005). Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Archives of internal medicine, 165(22), 2644-2650.

[8] Sohn, C., Kim, J., & Bae, W. (2012). The framingham risk score, diet, and inflammatory markers in Korean men with metabolic syndrome. Nutrition research and practice, 6(3), 246-253.

[9] Wilson, PWF., D'Agostino, RB., Levy D., Belanger AM., Silbershatz H., Kannel WB. (1998). Prediction of coronary heart disease using risk factor categories. Circulation, 97(18):1837–47.

[10] Yousefzadeh, G., Shokoohi, M., Najafipour, H., & Shadkamfarokhi, M. (2015). Applying the Framingham risk score for prediction of metabolic syndrome: The Kerman Coronary Artery Disease Risk Study, Iran. ARYA atherosclerosis, 11(3), 179.

[11] Hegazy, S. K., & NE, E. A. (2013). Leptin and c-reactive protein are implicated in pathogenesis of skin tag. Journal of Diabetes Research & Clinical Metabolism, 2-5.

[12] Kurniawati, Y., Devi, M., Yakub, K., Affandi, K., & Marlina, A. (2019, July). Correlation of serum lipid profile with leptin levels of skin tags patients. In Journal of Physics: Conference Series (Vol. 1246, No. 1, p. 012022). IOP Publishing.

[13] Fang, C. E. H., Crowe, C., Murphy, A., O'Donnell, M., & Finucane, F. M. (2020). Cross-sectional study of the association between skin tags and vascular risk factors in a bariatric clinic-based cohort of Irish adults with morbid obesity. *BMC research notes*, *13*(1), 1-6.

[14] Su, X., Luo, M., Tang, X., Luo, Y., Zheng, X., Peng, D., & CCC-ACS Investigators. (2019). Goals of non-high density lipoprotein cholesterol need to be adjusted in Chinese acute coronary syndrome patients: findings from the CCC-ACS project. Clinica Chimica Acta, 496, 48-54.

[15] González-Muniesa, P., Mártinez-González, M. A., Hu, F. B., Després, J. P., Matsuzawa, Y., Loos, R., Moreno, L. A., Bray, G. A., & Martinez, J. A. (2017). Obesity. Nature reviews. Disease primers, 3, 17034.

[16] Crujeiras, A. B., Carreira, M. C., Cabia, B., Andrade, S., Amil, M., & Casanueva, F. F. (2015). Leptin resistance in obesity: An epigenetic landscape. Life sciences, 140, 57-63.

[17] Su, X., Cheng, Y., & Chang, D. (2021). The Important Role of Leptin in Modulating the Risk of Dermatological Diseases. Frontiers in Immunology, 11, 3684.

[18] Nurhayati, R., Putra, I. B., & Siregar, R. (2019). Analysis of Serum Leptin Levels in Skin Tag Patients. Bali Medical Journal, 8(1), 376-379.

[19] El Safoury, O. S., Abdel Hay, R. M., Fawzy, M. M., Kadry, D., Amin, I. M., Abu Zeid, O. M., & Rashed, L. A. (2011). Skin tags, leptin, metabolic syndrome and change of the life style. Indian J Dermatol Venereol Leprol, 77(5), 577-80.

[20] Dopytalska, K., Baranowska-Bik, A., Roszkiewicz, M., Bik, W., & Walecka, I. (2020). The role of leptin in selected skin diseases. Lipids in Health and Disease, 19(1), 1-10.

[21] Shah, R., Jindal, A., & Patel, N. M. (2014). Acrochordons as a Cutaneous Sign of Metabolic Syndrome: A Case. Control Study. Annals of medical and health sciences research, 4(2), 202-205.

[22] Erdoğan, B. Ş., Aktan, Ş., Rota, S., Ergin, Ş., & Evliyaoğlu, D. (2005). Skin tags and atherosclerotic risk factors. The Journal of dermatology, 32(5), 371-375.

[23] King, C. C., Piper, M. E., Gepner, A. D., Fiore, M. C., Baker, T. B., & Stein, J. H. (2017). Longitudinal impact of smoking and smoking cessation on

inflammatory markers of cardiovascular disease risk. Arteriosclerosis, thrombosis, and vascular biology, 37(2), 374-379.

[24] McEvoy, J. W., Nasir, K., DeFilippis, A. P., Lima, J. A., Bluemke, D. A., Hundley, W. G., & Blaha, M. J. (2015). Relationship of cigarette smoking with inflammation and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology, 35(4), 1002-1010.

[25] Setayeshgar, S., Whiting, S. J., Pahwa, P., & Vatanparast, H. (2015). Predicted 10-year risk of cardiovascular disease among Canadian adults using modified Framingham Risk Score in association with dietary intake. Applied Physiology, Nutrition, and Metabolism, 40(10), 1068-1074.

[26] Artigao-Rodenas, L. M., Carbayo-Herencia, J. A., Divison-Garrote, J. A., Gil-Guillen, V. F., Massó-Orozco, J., Simarro-Rueda, M., & Grupo de Enfermedades Vasculares de Albacete (GEVA). (2013). Framingham risk score for prediction of cardiovascular diseases: a population-based study from southern Europe. PLoS One, 8(9), e73529.

[27] Kim, W. J., Kwon, C. H., Han, S., Lee, W. S., Kang, J. W., Ahn, J. M., & Park, S. J. (2016). Role of coronary artery calcium scoring in detection of coronary artery disease according to Framingham risk score in populations with low to intermediate risks. Journal of Korean medical science, 31(6), 902-908.

[28] Yang, W., Ma, R., Zhang, X., Guo, H., He, J., Mao, L., & Guo, S. (2018). Comparison between metabolic syndrome and the Framingham risk score as predictors of cardiovascular diseases among Kazakhs in Xinjiang. Scientific reports, 8(1), 1-8.

[29] Zhang, X. L., Wan, G., Yuan, M. X., Yang, G. R., Fu, H. J., Zhu, L. X., & Yuan, S. Y. (2020). Improved Framingham risk scores of patients with type 2 diabetes mellitus in the Beijing community: a 10-year prospective study of the effects of multifactorial interventions on cardiovascular risk factors (the Beijing Communities Diabetes Study 22). Diabetes Therapy, *11*(4), 885-903.

[30] Kutty, P. K., & Kutty, M. K. (2021). Obesity and Skin Problems. In Obesity and its Impact on Health (pp. 25-48). Springer, Singapore.