Comparative study of cortisol and leptin concentration in obese non-diabetics and obese with uncomplicated diabetes.

Article · January 2020

CITATIONS
0

READS
22

9 authors, including:

Adela H Elamami
University of Benghazi
38 PUBLICATIONS **46** CITATIONS
SEE PROFILE

Ahmed Zakoko
University of Nottingham
12 PUBLICATIONS **6** CITATIONS
SEE PROFILE

Mustafa Y. G. Younis
University of Benghazi
37 PUBLICATIONS **190** CITATIONS
SEE PROFILE

Farag Elshaari
University of Benghazi
33 PUBLICATIONS **135** CITATIONS
SEE PROFILE

Libyan Journal of Science & Technology 12:1 (2020) 181–186

Faculty of Science - University of Benghazi

Libyan Journal of Science & Technology

journal home page: www.sc.uob.edu.ly/pages/page/77

Comparative study of cortisol and leptin concentration in obese non-diabetics and obese with uncomplicated diabetes.

Siba Z. Tariq[a], Adella B El-amamy[b], Ahmed M. Zakoko[a], Salah A. Awad[a], Mustafa Y. Younis[a], Ahmed A. Benhasouna[c], Khaled A. El Gehani[c], Farag A. Elshaari[a,*]

[a]*Department of Biochemistry, Faculty of Medicine, University of Benghazi*

[b]*Department of Internal Medicine, Faculty of Medicine, University of Benghazi*

[c]*Department of Pathology, Faculty of Medicine, University of Benghazi*

Highlights

- **Obesity is related to leptin hormone regardless of the presence of diabetes, and the use of metformin.**
- **No evident changes were noted in serum cortisol activity between the obese diabetic and non-diabetics irrespective of FBS differences.**
- **$HbA1_C$ is the main determinant of lipoprotein disruption, thus keeping blood sugar under control is an established primacy in clinical lipid management routines.**

ARTICLE INFO

Article history:

Received 31 May 2020
Revised 24 December 2020
Accepted 28 December 2020

Keywords:

Diabetes, Obesity, WC, BMI, Cortisol, Leptin

**Address of correspondence:*

E-mail address: Farag.elshaari@uob.edu.ly

F. A. Elshaari

ABSTRACT

In addition to chronic hyperglycemia, the main characteristic feature of diabetes is the impairment of carbohydrate, fat, and protein metabolism that underline the main cause of short-term and late-developing disease complications. These lead to stern changes in body systems, notably, the increased activity of the hypothalamic-pituitary-adrenal (HPA) axis, and expectedly, the upstream/downstream changes in adipokines and cortisol. This study was undertaken to assess cortisol and leptin levels in relation to obesity and diabetes. Excluding patients with complications, twenty-eight obese type 2 diabetic patients (diabetes duration less than 10 years) were recruited for the study. All patients were receiving metformin doses of 500 mg or 850 mg.

The controls included in the study were 16 non-diabetic apparently healthy obese volunteers. Fasting blood sugar (FBS), HbA1C, LDL, HDL, leptin, and cortisol were analyzed. In the diabetic group FBS, HbA1C, TAG, LDL, and total cholesterol were significantly higher compared to the obese non-diabetic group. Serum leptin and cortisol showed no significant differences between the diabetic and the obese control group at 95% confidence. However, in the diabetic group, significant correlations were seen between serum leptin and HDL, and strong correlations relating the bodyweight indicators (BMI; WC) with leptin and cholesterol. These results were expected to be the outcome of the cortisol changes in type2 diabetes, but no significant correlations were evident between serum cortisol and HbA1c. The outcome of the study was explained relating the similarity of the hormone's activity to the patients included in the study have had the disease for considerably short periods and were selected for lacking the complications usually seen in chronic long-duration diabetes.

1. Introduction

In diabetes, short and late-term complications caused by persistent hyperglycemia leave serious effects on body systems. These effects, seen in patients showing endocrine and autonomic nervous system (ANS) imbalance, are reflected in the raised activity of the hypothalamic-pituitary-adrenal (HPA) axis resulting in hypercortisolism. In addition, it has been found that the dysfunctional level of the HPA axis in diabetic patients is linked with the damage of the neuronal pathway of the axis, and with the damage resulting in the weakening response of glucocorticoids negative feedback (Elahi-Moghaddam *et al*., 2013).

In many studies, abdominal adiposity was found to be one of the strong predictors of type 2 diabetes, and maybe an indicator for the dysfunctional adipose tissue that is often accompanied by metabolic disturbances including insulin resistance, hypertriglyceridemia, hyperinsulinemia, glucose intolerance, hypertension, reduced level of HDL, and increased small and dense LDL (Lin and Sun, 2010). Several research groups reported that all these disturbances were linked to adipocytokines metabolic disruptions. Such adipocytokines include leptin, a peptide hormone that influences energy homeostasis, immune, and endocrine function. High serum leptin is a characteristic feature found in most obese individuals, but due to the decreased leptin transport into the central nervous system, they show leptin resistance (Bahathiq and Omar, 2010).

Alteration in the endocrine glands involved in regulating body metabolism is a result of diabetes-caused dysfunctions in the general body metabolism, and this further complicates the problem of metabolic disruption. On the other hand, diabetic patients' state of health is known to deteriorate due to neuropathy, the most common neurological complication of diabetes, through its effect on the endocrine system, and the peripheral and autonomic nervous systems (Edwards *et al*., 2008).

The activity of the hypothalamic-pituitary-adrenal axis (HPA) is known to increase in patients with diabetes due to autonomic

 ISSN 2663-1407; National Library of Libya, Legal number: 390/2018

nervous system imbalance, and this is a consequence of hypercortisolism and adrenocortical growth. These alterations are believed to result from the reduction in glucocorticoid feedback relative sensitivity along with the different parts of the axis, such as the changes in 11- beta hydroxy-steroid dehydrogenase (11B-HSD) enzyme activity, and the elevated hypothalamus expression of corticotropin-releasing hormone (Barber *et al*., 2003).

The lipoprotein lipase mediated hydrolysis and uptake of circulating triglycerides and fatty acids (FAs) into adipocytes are thought to be enhanced by glucocorticoids (GCs) exposure. This effect is believed to be more evident in the trunk subcutaneous and visceral adipose tissue depots. However, the reason for such specific depot LPL activity is unaccounted for (Geer *et al*., 2014). Furthermore, there are well defined contradictory effects in lipid metabolism occurring as a result of several mechanisms induced by GCs as well as other mechanisms that remain to be elucidated (Peckett *et al*., 2011)

The present study was undertaken to assess serum concentration of cortisol and leptin and their possible effects relative to metabolic disruptions caused by type 2 diabetes and/or obesity, which may contribute to the outcome of such diseases.

2. Patients and methods:

2.1. Subjects

In the current study 28 obese type, 2 diabetic patients (diabetes duration less than 10years) were included. The selected patients were receiving metformin treatment in special daily doses of 500mg or 850mg. Patients with complications were excluded from the study. The controls were 16 non-diabetic apparently healthy obese volunteers. All the study participants were asked to answer a case history questionnaire, all of them had their height, weight, waist circumference measured, and body mass index (kg/m^2) calculated. They were asked to fast for 12 hours to have their blood samples submitted to biochemical analysis for FBS, HbA1$_C$, LDL, HDL, Leptin, and Cortisol .

2.2. Blood collection

Blood was collected via venipunctures. It was split into EDTA and plain tubes. Plain tubes were left at room temperature for coagulation. The serum samples were collected following centrifugation at 3,300×g, 4°C for 10 min and stored at −20°C until analyzed. Serum samples were used for the estimation of total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), Triacylglycerols (TAG), serum cortisol, and Leptin. The whole blood was analyzed for HbA1C and fasting blood sugar (FBS) at the time of sample collection.

2.3. Anthropometric Measurements

Body mass index (BMI) was calculated as weight in kg/m^2 of height. Weight was measured using SECA scale (150 kg). Waist circumference was measured using an anthropometer. The tape was placed midway between the bottom line of the ribs and the top of the hip bone. The study volunteers were asked to breathe out normally and the measurements were taken in centimeters.

2.4. Biochemical Measurements

Lipoproeins: The serum levels of TC, TG, HDL-C, LDL-C were determined using the respective assay kits in accordance with the manufacturer's instructions. All samples were detected by COBAS INTEGRA ®400 (Roche Diagnostics, Switzerland).

2.5. Fasting blood sugar (FBS)

Quantitative determination of glucose was carried out by COBAS INTEGRA ®400 (Roche Diagnostics, Switzerland).

2.6. Hemoglobin A1$_C$ (HbA1$_C$)

HbA1$_C$ in whole blood was estimated by fluorescence Immunoassay ichroma™ for the quantitative estimation of HbA1$_C$ in whole blood (Boditech Med Inc., Republic of Korea).

2.7. Measurement of Hormone Level

Leptin concentration was analysed using Human Leptin ELISA kit (Biovendor Research and Diagnostic Products, Germany). The ELISA estimation was run using the automated instrument of Chem Well Models 2902 and 2910 washer-reader (Awareness Technology Inc., Germany). Cortisol was estimated using the fluorescence immunoassay I chroma™ (Boditech Med Inc., Republic of Korea).

2.8. Statistical analysis

The presented data are shown as the mean ± standard deviation. The means were compared using the student's T-test and relationship extents were measured using Pearson's test. P<0.05 was considered to indicate statistically significant differences. Statistical analysis for the selected measurements and tests was carried out using the SPSS version 17.0 software (SPSS, Inc., USA).

3. Results

The anthropometric measurement of the diabetic obese group and the obese control group are summarized in Table 1. All, Age, BMI, waist circumference showed no significant statistical differences between the obese diabetics and the obese non-diabetic patients.

Table1

Mean ± SD of Age, BMI, and WC in control and diabetic patient

Parameter	Control N=6		Patient N=28		P
	Mean	S.D	Mean	S.D	
Age	32.93	5.39	46.71	6.38	0.276
BMI	31.6	6.76	33.41	6.91	0.735
WC	113.18	20.48	116.89	15.98	0.091

In the diabetic group FBS, HbA1$_C$, TAG, LDL, and TC were significantly higher compared to the obese non-diabetic group. On the contrary HDL showed no difference comparing the two groups (Table 2 and 3).

Table 2

Mean ±SD of serum HbA1$_C$and FBS in control and diabetic patients

Parameter	**Control (N=16)**		**Patient (N=28)**		**P**
	Mean	**S.D**	**Mean**	**S.D**	
HbA1C	5.193	0.4	7.97	1.35	0.000**
FBS	101.93	16.97	158.89	55.24	0.002**

**P highly significant at p<0.01

Table 3

Mean ± SD of serum Cholesterol, LDL, HDL and TG in control and diabetics

Parameter	**Control (N=16)**		**Patient (N=28)**		**P**
	Mean	**S.D**	**Mean**	**S.D**	
Total cholestrol	128.4	20.55	166.5	35.78	0.012*
LDL	63.56	15.19	83.28	41	0.019*
HDL	36	7.1	36.28	8.84	0.239
TG	69.125	22.22	138.89	59.37	0.038*

*P significant at p<0.05

No significant differences (p>0.05) were observed in serum leptin and cortisol between the diabetic group and the obese control group as shown in (Table 4).

Table 4

Mean ± SD of serum Leptin and cortisol in control and diabetic patient

Parameter	Control (N=16)		Patient (N=28)		P
	Mean	S.D	Mean	S.D	
Serum Leptin (ng/mL)	5.09	1.73	4.05	1	0.072
Serum Corti-sol (nmol/L)	295.66	64.14	322.34	79.78	0.592

In both groups, BMI was significantly correlated with WC, and FBS was significantly correlated with $HbA1_C$. Similarly, in both groups, a significant correlation was evident between serum leptin and waist circumference and this correlation was higher in the control group (Table 5).

Table 5

Significant Correlation (r) within the obese non-diabetic group

Parameters	Correlation	Leptin	WC	TC	HDL
Wt	R	0.698**	0.981**		
	P	0.003	0.000		
BMI	R	0.741**	0.877**	0.626**	
	P	0.001	0.000	0.009	
WC	R	0.769**			
	P	0.000			
TAG	R			0.493*	
	P			0.05	
LDL	R				−0.454
	P				0.078

In the diabetic group, significant correlations were seen between serum leptin and HDL. Low-density lipoproteins were highly correlated with $HbA1_C$ and TC (Table 6). In addition, cholesterol was significantly correlated with serum $HbA1_C$, HDL, and LDL. There was a moderate correlation between TAG and $HbA1_C$ (Table 6). Most of these correlations were not seen in the obese non-diabetic group with the exception of the strong correlations seen between the bodyweight indicators (BMI; WC), leptin, and TC (Tables 5 and 6).

Table 6

Significant Correlation (r) within the obese diabetic group

Parameters	Correlation	WC	HbA1C	FBS	LDL	HDL	TSG
HBA1C	r			0.495**	0.616**		0.367
	P			0.007**	0.000		0.05*
Leptin	r	0.415*				0.392*	
	P	0.028				0.039	
BMI	r	0.685**					
	P	0.000					
Cholesterol	r		0.433*		0.661**	0.508**	
	P		0.021		0.000	0.006	

4. Discussion

When the level of insulin and glucocorticoids enhance the release of fatty acids from adipocytes, the synthesis of lipoproteins in liver cells is increased, and subsequently fatty liver occurs. Insulin resistance and the impaired intracellular insulin signaling are the eventual results of such changes (Vegiopoulos and Herzig, 2007). Thus, the elevated levels of blood lipids are believed to be the cause of the decreased sensitivity of adipocytes to insulin, and the changing levels of glucocorticoids and insulin activity (Vergès, 2009).

It is established that under physiological conditions the HPA axis activity is influenced by the negative feedback of glucocorticoids (Herman *et al.* 2016). Therefore, the sensitivity of this axis is reduced due to its hormonal feedback during chronic glucocorticoids increase. The functional impairments and increased activity of HPA axis in hyperglycemic conditions are believed to be, at least in part, the outcome of such reduced sensitivity.

Research in the pathogenesis of prevalent diseases such as cardiovascular disease and Type 2 diabetes places metabolic trepidations central to other changes. In addition, most of these metabolic irregularities turn out to be the results of endocrine disturbances on a neuroendocrine basis, and insulin resistance may occupy a pivital role. When the regulation capability of the neuroendocrine played by the HPA axis is overwhelmed abnormalities will occur. Even moderate abnormalities in these central regulatory systems may, in the long run, lead to disease (Miller, 2018). Thus, under hyperglycemic conditions, such findings collectively point to the effect on HPA axis activity and consequently the hormonal output of the adrenal cortex, especially in type 2 diabetes (Chiodini *et al*, 2007). Hence, the incidence of secondary dysfunction in other endocrine glands activity, and subsequently the exacerbation and complication of disease if no control of blood glucose is achieved, are the eventual outcome of such effects. Furthermore, the strong stimulation of the adrenal cortex, hypertrophy, and elevated hormonal output is apparently the subsequent effect of the increase in ACTH levels. In our study, the observed mean serum cortisol appeared non-significantly different in diabetic patients compared to control (P>0.05). In addition, there was no significant correlation between serum cortisol and HbA1C in obese diabetic patients. This finding is reasonable because the patients in the current study did not reach critical chronic hyperglycemia exposure as reflected in their levels of FBS and HbA1C.On the other hand, other causes of an increased volume of adrenal cortex and cortisol secretion that could be considered include impaired lipid metabolism and insulin resistance (Golden *et al*., 2007, Saravia *et al*., 2001). However, patients included in our study did not suffer from critical dyslipidemia. It has been agreed upon that insulin resistance is an integral feature of metabolic syndrome, and is considered as a key predictor of the development of type 2 diabetes (Roberts *et al*., 2013). In addition, it has long been recognized that there is a strong association between obesity and type 2 diabetes, and the focus of this link is the role believed to be played by obesity in the induction of insulin resistance. In our study, obesity was expressed using BMI and WC to detect general and abdominal obesity. In both, the diabetics and non-diabetics, we found a strong significant correlation

between BMI and WC, which was higher in controls than in diabetics. Such a difference could be owed to the effect of metformin taken by diabetic patients. The support for this observation is provided by a UK study conducted to explore the effect of anti-diabetic treatment on body weight in obese patients (krentz, 2006). Similarly, in our study, the selected patients did not have any common diabetes-related complications. The mentioned UK study was carried out to assess whether metformin has an effect on obesity and related pathological condition such as myocardial infarction and diabetes-related mortality. The study showed that patients having a controlled diet and receiving metformin therapy showed a reduction of 39% in MI incidence, 42% in diabetes-related mortality, and 31% in prevention of the risk of diabetes. Insulin associated weight gain can potentially be reduced through the co-administration of metformin with insulin. The underlying mechanisms with which metformin neutralizes the weight gain in this context is poorly understood.

Excessive fat accumulation promotes the release of free fatty acids into the circulation from adipocytes, which may be a critical factor in modulating insulin sensitivity (Sears and Perry, 2015). However, plasma free fatty acids levels do not increase in proportion to the amount of body fat, since the basal adipose tissue lipolysis per kilogram of fat is lower in obese subjects than in lean subjects (Rydén *et al*., 2013, Sears and Perry, 2015), and it was shown to be associated with the down-regulation of hormone-sensitive lipase and adipose triglyceride lipase, key enzymes involved in intracellular degradation of triglycerides (McQuaid *et al*., 2011; Jocken *et al*., 2007). Thus, Karpe *et al*., (2011) suggested that the link between circulating free fatty acids levels and insulin sensitivity in vivo needs further investigation to elucidate the details of such a complicated relationship. In addition to hypertrophy of adipocytes, obesity and insulin resistance involves the expansion of the extracellular matrix and cells other than adipocytes such as endothelial cells, stromal vascular cells, macrophages, and monocytes (Varma *et al*., 2008, Pasarica *et al*., 2009). A recent study showed that adipose tissue from obese insulin-sensitive individuals had larger blood vessels, but decreased capillary density as compared to adipose tissue from lean insulin-sensitive individuals. This suggests that altered angiogenesis and oxygen delivery may play a role in obesity (Lawler *et al*., 2016).

In our study, there was a strong positive correlation between BMI (as a detector of obesity) and serum cholesterol in obese non-diabetic control patients, but this correlation was not found in obese diabetic patients. The literature shows the inconsistency of results regarding the influence of metformin on lipid profile. Some studies reported a reduction in TC levels only, while others reported a reduction of TC and TG with an increase in HDL-C, still, other studies showed no changes in lipid profile. In a recent study, Lin *et al*. (2018) showed that in patients newly diagnosed with T2DM, metformin therapy without concomitant usage of lipid-lowering drugs significantly decreased both serum LDL-C and TG, as well as increased HDL-C levels. It has been concluded that more studies are needed to clarify this issue (Mourão-Júnior *et al*., 2006, Lin *et al*., 2018).

Several studies have demonstrated that in order to prevent the development and progression of chronic complications of diabetes, a comprehensive patient assessment approach to all elements of the metabolic syndrome is required (Cornier *et al*. 2008). However, whenever sophisticated laboratory methods are not available, WC a feature considered as one major clinical assessment factor of the metabolic syndrome should be considered (Huang, 2009, Grundy *et al*., 2005).

In our study, we measured serum leptin for both the obese non-diabetic and obese diabetic patients. It was surprisingly found that there was a strong correlation between BMI and serum leptin in obese non-diabetics, and this correlation was not found in diabetic patients even though the means of BMI of the groups were closely similar. These results are supported by a study by Zhu and his co-workers (2013) in which they assessed the difference in the effect of glimeperide and metformin on obese diabetic patients. The highest serum insulin concentration and insulin resistance levels were clearly reported in glimepiride treated group as compared to the control and metformin-treated group (Zhu *et al*., 2013).

Leptin levels in our study showed no significant differences between the studied groups. This is supported by several studies in recent years presenting the role of body weight as a major determinant of circulating leptin levels. These studies showed that leptin as one of the potential mediators of inflammation can be partly responsible for the pathogenesis of autoimmune diseases and other inflammatory disorders. Thus, leptin increase following chronic inflammatory processes as a result of such diseases or metabolic disorder can further fuel the inflammatory state even though many aspects of the interaction process between leptin and inflammation is still unclear (Bjornstad *et al*., 2018, Pérez-Pérez *et al*., 2014, Elshaari *et al*., 2018).

Several studies show that metformin (1, 1 dimethyl biguanide) enhances glucose transport and utilization, mitochondrial and peroxisomal FA β-oxidation, basal lipolysis, aerobic and anaerobic respiration, in addition to leptin secretion reduction prior to weight loss. Collectively, these metabolic effects pushed scientists to advocate that adipose monitoring signals over the long term are expected to play the role of second messengers that influence the metformin effect on food intake. This is deeply rooted by the rise in insulin sensitivity following metformin treatment, and by the action of insulin on energy status signals regulating adiposity (Attia *et al*., 2001, Rena *et al*., 2017).

Inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) is a strategy that has been proposed to suppress glucocorticoid action in a tissue-specific manner. Several varieties of 11βHSD1 inhibitors are now under investigation to treat type 2 diabetes and obesity. Such intended inhibition is considered an attractive therapeutic target for treating T2DM and obesity, with significant potential advantages over existing treatment options (Anagnostis *et al*., 2013). During last year, 2019, Koike *et al*. (2019) discovered a novel 11βHSD1 inhibitor with potent and selective inhibitory activity against human 11β-HSD1. This inhibitor showed metabolic stability against human and mouse liver microsomes. Oral administration of this novel 11βHSD1 inhibitor to diabetic ob/ob mice reduced corticosterone levels in adipose tissue, and thereby reduced plasma glucose and insulin levels in a dose-dependent manner (Koike *et al*., 2019). These research themes and discoveries point to the importance of studying glucocorticoids and their relation to other regulatory factors such as leptin, the target of the current study. More importantly, it has been noted that there is no clear increase in serum cortisol in obese human subjects, but there is increased activation of cortisol from cortisone within local adipose tissue (Lee *et al*., 2008).

5. Conclusions

The current study was undertaken assuming that the metabolic dysregulations seen in diabetes are the result of the relationship between elevated serum cortisol and other metabolic changes. Although, no significant correlations were seen in the current study between serum cortisol and $HbA1_C$, the biochemical changes and relationships reported here are related to the criteria of the selection of the patients. Thus, by excluding patients with long duration of diabetes (>10 years), and those with complications commonly seen in chronic diabetic patients, the consequences caused by exposure to chronic cortisol could not be seen. The significant relationship between elevated cortisol and type 2 diabetes were previously reported in patients that had the disease for periods longer than 10 years with or without complications. Currently, diabetes is an extremely complicated metabolic disease that involves several pathways and numerous factors that can be affected by antidiabetic drugs. Thus, the relashionship of leptin to obesity indicators seen in the obese controls and absent in the diabetic patients on daily metformin highlights such a complicated process.

References

Anagnostis, P., Katsiki, N., Adamidou, F., Athyros, V. G., Karagiannis, A., Kita, M., Mikhailidis, D. P. (2013) '11beta-Hydroxysteroid dehydrogenase type 1 inhibitors: novel agents for the treatment of metabolic syndrome and obesity-related disorders?', *Metab. Clin. Exp*., 62(1), pp. 21–33.

Attia, G. R., Rainey, W. E., Carr, B. R. (2001) 'Metformin directly inhibits androgen production in human thecal cells', *Fertil Steril,* 76, pp. 517-24.

Bahathiq, S., Omar, A. (2010) 'Relationship of Leptin Hormones with Body Mass Index and Waist Circumference in Saudi Female Population of the Makkah Community', *Open Obes. J.,* 2, pp. 95-100.

Barber, M., Kasturi, B., Austin, M., Patel, K., Mohankumar, S., Mohankumar, P. (2003)'Diabetes-induced neuroendocrine changes in rats: Role of brain monoamines, insulin and leptin', *Brain res.,* 964, pp. 128-35.

Bjornstad, P., Schäfer, M., Truong, U., Cree-Green, M., Pyle, L., Baumgartner, A., Garcia Reyes, Y., Maniatis, A., Nayak, S., Wadwa, R. P., Browne, L. P., Reusch, J. E. B., Nadeau, K. J. (2018) 'Metformin Improves Insulin Sensitivity and Vascular Health in Youth With Type 1 Diabetes Mellitus', *Circulation,* 138, pp. 2895-2907.

Chiodini, I., Adda, G., Scillitani, A., Coletti, F., Morelli, V., Di Lembo, S., Epaminonda, P., Masserini, B., Beck-Peccoz, P., Orsi, E., Ambrosi, B., Arosio, M. (2007) 'Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications', *Diabetes Care,* 30, pp. 83-8.

Cornier, M.-A., Dabelea, D., Hernandez, T. L., Lindstrom, R. C., Steig, A. J., Stob, N. R., Van Pelt, R. E., Wang, H., Eckel, R. H. (2008) 'The Metabolic Syndrome', *Endocr. Rev.,* 29, pp. 777-822.

Edwards, J. L., Vincent, A. M., Cheng, H. T., Feldman, E. L. (2008) 'Diabetic neuropathy: mechanisms to management',*Pharmacol. Ther.,* 120, pp. 1-34.

Elahi-Moghaddam, Z., Behnam-Rassouli, M., Mahdavi-Shahri, N., Hajinejad-Boshroue, R., Khajouee, E. (2013) 'Comparative study on the effects of type 1 and type 2 diabetes on structural changes and hormonal output of the adrenal cortex in male Wistar rats', *J. Diabetes Metab. Disord.,* 12, pp. 9-9.

Elhawari, H., Elshaari, F., Bugaigis, H., Younis, M., Elbadri, A., Abdalla, H., Biswas, S., Rawal, A. K., Fakruddin, D., Srikumar, S., Min, Y., Vedangi, A., Argi, A., Elbarassi, I., Hussain, A., Tun, K., Peela, L. T., Peela, J. R. (2018) 'Leptin and Adiponectin and their Relationship to Drugs, Hypertension, Diabetes, and Body Mass Index in Left Ventricular Heart Failure Patients', *ECNU*., 137, pp. 519-526.

Geer, E. B., Islam, J., & Buettner, C. (2014) 'Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism', *Endocrinol. Metab. Clin. North Am.*, *43*(1), pp. 75–102.

Golden, S. H., Malhotra, S., Wand, G. S., Brancati, F. L., Ford, D. Horton, K. (2007) 'Adrenal Gland Volume and Dexamethasone-Suppressed Cortisol Correlate with Total Daily Salivary Cortisol in African-American Women', *J. Clin. Endocrinol. Metab.,* 92, pp. 1358-1363.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., Gordon, D. J., Krauss, R. M., Savage, P. J., Smith, S. C., Jr., Spertus, J. A., Costa, F. (2005) 'Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement', *Circulation,* 112, pp. 2735-52.

Herman, J. P., Mcklveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., Myers, B. (2016) 'Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response', *Compr Physiol,* 6, pp. 603-21.

Huang, P. L. (2009) 'A comprehensive definition for metabolic syndrome', *Dis Model Mech,* 2, pp. 231-7.

Jocken, J. W. E., Langin, D., Smit, E., Saris, W. H. M., Valle, C., Hul, G. B., Holm, C., Arner, P., Blaak, E. E.(2007) 'Adipose Triglyceride Lipase and Hormone-Sensitive Lipase Protein Expression Is Decreased in the Obese Insulin-Resistant State', *J. Clin. Endocrinol. Metab.,* 92, pp. 2292-2299.

Karpe, F., Dickmann, J. R., Frayn, K. N. (2011) 'Fatty acids, obesity, and insulin resistance: time for a reevaluation', *Diabetes,* 60, pp. 2441-9.

Koike, T., Shiraki, R., Sasuga, D., Hosaka, M., Kawano, T., Fukudome, H., Kurosawa, K., Moritomo, A., Mimasu, S., Ishii, H., Yoshimura, S.(2019) 'Discovery and Biological Evaluation of Potent and Orally Active Human 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors for the Treatment of Type 2 Diabetes Mellitus', *Chem Pharm Bull (Tokyo),* 67, pp. 824-838.

Krentz, A. J. (2006) 'Comparative safety of newer oral antidiabetic drugs', *Expert Opin Drug Saf.,* 5, pp. 827-834.

Lawler, H. M., Underkofler, C. M., Kern, P. A., Erickson, C., Bredbeck, B., Rasouli, N. (2016) 'Adipose Tissue Hypoxia, Inflammation, and Fibrosis in Obese Insulin-Sensitive and Obese Insulin-Resistant Subjects', *J Clin Endocrinol Metab,* 101, pp. 1422-8.

Lee, M. J., Fried, S. K., Mundt, S. S., Wang, Y., Sullivan, S., Stefanni, A., Daugherty, B. L., Hermanowski-Vosatka, A. (2008) 'Depot-specific regulation of the conversion of cortisone to cortisol in human adipose tissue', *Obesity (Silver Spring, Md.)*, 16(6), pp. 1178–1185.

Lin, S. H., Cheng, P. C., Tu, S. T., Hsu, S. R., Cheng, Y. C., Liu, Y. H. (2018) 'Effect of metformin monotherapy on serum lipid profile in statin-naïve individuals with newly diagnosed type 2 diabetes mellitus: a cohort study', *Peer J.,* 6, pp. e4578.

Lin, Y., Sun, Z. (2010) 'Current views on type 2 diabetes', *J. Endocrinol,* 204, pp. 1-11.

Mcquaid, S. E., Hodson, L., Neville, M. J., Dennis, A. L., Cheeseman, J., Humphreys, S. M., Ruge, T., Gilbert, M., Fielding, B. A., Frayn, K. N., Karpe, F. (2011) 'Downregulation of adipose tissue fatty acid trafficking in obesity: a driver for ectopic fat deposition?', *Diabetes,* 60, pp. 47-55.

Miller, W. L. (2018)'The Hypothalamic-Pituitary-Adrenal Axis: A Brief History', *Horm Res Paediatr.*, *89*(4), pp. 212–223.

Mourão-Júnior, C. A., Sá, J. R., Guedes, O. M. S., Dib, S. A. (2006) 'Effects of metformin on the glycemic control, lipid profile, and arterial blood pressure of type 2 diabetic patients with metabolic syndrome already on insulin', *Braz. J. Med. Biol. Res.,* 39, pp. 489-494.

Pasarica, M., Gowronska-Kozak, B., Burk, D., Remedios, I., Hymel, D., Gimble, J., Ravussin, E., Bray, G. A., Smith, S. R. (2009) 'Adipose Tissue Collagen VI in Obesity', *J. Clin. Endocrinol. Metab.,* 94, pp. 5155-5162.

Peckett, A. J., Wright, D. C., Riddell, M. C. (2011) 'The effects of glucocorticoids on adipose tissue lipid metabolism', *Metab. Clin. Exp.*, 60(11), pp. 1500–1510.

Pérez-Pérez, A., Sánchez-Jiménez, F., Vilariño-García, T., Sánchez-Margalet, V. (2020) 'Role of Leptin in Inflammation and Vice Versa', *Int. J. Mol. Sci.,* 21, 5887.

Rena, G., Hardie, D. G., Pearson, E. R. (2017) 'The mechanisms of action of metformin', *Diabetologia,* 60, pp. 1577-1585.

Roberts, C. K., Hevener, A. L., Barnard, R. J. (2013) 'Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training', *Compr Physiol*, 3, pp. 1-58.

Rydén, M., Andersson, D. P., Bernard, S., Spalding, K., Arner, P. (2013) 'Adipocyte triglyceride turnover and lipolysis in lean and overweight subjects', *J. Lipid Res.*, 54(10), pp. 2909–2913.

Saravia F. E., Gonzalez S. L., Roig P., Alves V., Homo-Delarche F., De Nicola A. F. (2001) 'Diabetes increases the expression of hypothalamic neuropeptides in a spontaneous model of type I diabetes, the nonobese diabetic (NOD) mouse', *Cell Mol Neurobiol*, 21(1), pp. 15-27.

Sears, B., Perry, M. (2015) 'The role of fatty acids in insulin resistance', *Lipids Health Dis.*, 14, pp. 121.

Varma, V., Yao-Borengasser, A., Bodles, A. M., Rasouli, N., Phanavanh, B., Nolen, G. T., Kern, E. M., Nagarajan, R., Spencer, H. J., Lee, M.-J., Fried, S. K., Mcgehee, R. E., Peterson, C. A., Kern, P. A.(2008) 'Thrombospondin-1 Is an Adipokine Associated With Obesity, Adipose Inflammation, and Insulin Resistance', *Diabetes,* 57, pp. 432-439.

Vegiopoulos, A., Herzig, S. (2007) 'Glucocorticoids, metabolism and metabolic diseases', *Mol. Cell. Endocrinol.,* 275, pp. 43-61.

Vergès, B. (2009)'Lipid disorders in type 1 diabetes',*Diabetes Metab,* 35, pp. 353-60.

Zhu, H., Zhu, S., Zhang, X., Guo, Y., Shi, Y., Chen, Z., Leung, S. W. (2013) 'Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials', *Diabetol Metab Syndr,* 5, pp. 70