https://doi.org/10.37939/jrmc.v28i3.2631

Comparison Of Glucagon Like Peptide/1 Levels In Diabetic Women With Ovarian Polycystic Syndrome And Healthy Women

Namra Iqtidar[1], Imran Ali Zaidi[2], Sobia Niaz[3], Javaria Latif[4], Amir Naveed[5], Ayesha Yousaf[6]

Abstract

Objective: The aim of the study is to compare Glucagon-Like Peptide-1 levels in polycystic ovarian syndrome patients having diabetes mellitus (DM) and healthy women.Polycystic ovarian syndrome (PCOS) is one of the routine endocrinological disorders of reproductive-aged women and it is associated with many problems and complications later in life. A relatively novel peptide hormone which is included in incretins (Gut-derived hormones) is Glucagon-like peptide-1(GLP-1). This gut cells-derived peptide hormone originates from L cells which are endocrine cells in the intestine. The receptors of GLP-1 hormones are found in multiple places. Mostly it is found in islet pancreatic beta-cells, in the brain, in the cardiovascular system, and the lungs. The main function of GLP-1 is the reduction of glucose blood levels during hyper-glycemia through the mechanism of increased secretion of hormone insulin and reduced glucagon hormone secretion. GLP-1 promotes satiation and slows up stomach emptying, and hence reduces post-meal glucose blood levels. Moreover, GLP-1 is required to significantly stimulate GnRH (Gonadotropin Hormone releasing hormone) secretion because of the presence of GLP-1 brain receptors located on the GnRH neurons which cause more LH (Luteinizing hormone) secretion.

Methods: A total of 104 subjects participated in the study. Out of them, 52 had PCOS with DM (Group 2), and 52 were age and weight-matched healthy subjects (Group 1) with no signs of hormonal abnormalities.

Results: Mean ± SD of GLP-1 levels in healthy women was 0.41± 0.04 ng/dl as compared to 0.18± 0.03 ng/dl levels in PCOS with DM (p= <0.05). Mean Fasting blood sugar levels in healthy women were 99.92 ± 4.46 mg/dl as compared to 150.19 ± 30.20 mg/dl in PCOS with DM (p= <0.05).

Conclusion: The study shows low GLP-1 levels are seen in PCOS with DM as compared to healthy women.

MeSH Keywords: polycystic ovarian syndrome, diabetes mellitus, Glucagon-Like Peptide -1(GLP-1)

[1] Consultant Gynaecologist, THQ Hospital, Kalabagh, Mianwali; [2] Assistant Professor Biochemistry, FMH College of Medicine and Dentistry, Lahore; [3] Associate Professor Physiology, Gujranwala Medical College; [4] Associate Professor Physiology, CMH Institute of Medical Sciences, Bahawalpur; [5] Professor Forensic Medicine, Amna Inayat Medical College; [6] Professor/HOD Anatomy, Rawalpindi Medical University.

Correspondence: Dr. Amir Naveed, Professor Forensic Medicine, Amna Inayat Medical College. **Email:** aamirnaveed865@gmail.com

Cite this Article: Iqtidar N, Zaidi IA, Niaz S, Latif J, Naveed A, Yousaf A. Comparison Of Glucagon Like Peptide/1 Levels In Diabetic Women With Ovarian Polycystic Syndrome And Healthy Women. JRMC. 2024 Sep. 27;28(3).517-521. https://doi.org/10.37939/jrmc.v28i3.2631.

Received February 22, 2024; accepted August 29, 2024; published online September 26, 2024

1. Introduction

Polycystic ovarian syndrome 'PCOS' is an internationally recognized endocrinological and metabolic problem among conceptive age women. This disorder is recognized by three main characteristics: asymmetrical and irregular menstruation cycle, hyperandrogenism, and polycystic ovarian anatomy. The worldwide distribution and prevalence of polycystic ovarian syndrome is said to be around 5%–20%. Despite recent advancements in diagnosis criteria and medical technology, PCOS has not been fully evaluated in terms of medical management. The features of PCOS affect a woman's life extensively beginning from the conceptive phase and even spanning in years after menopause.[1]

Polycystic ovarian syndrome (PCOS) is a complicated, familial, and poly-genetic disorder. The Rotterdam consensus criteria are routinely utilized to correctly diagnose PCOS. This criterion includes the presence of two out of three features that is oligo-anovulation, polycystic ovaries, and hyperandrogenism. Lifestyle modifications are the first-choice management of PCOS. The treatment strategy for uneven menstruation and excessive hair growth (hirsutism) is mainly decided as per patient need and clinical outcome. Along with managing the signs and symptoms of PCOS, it is necessary to first screen and then treat the co-morbid issues widely seen with PCOS, such as type-2 diabetes mellitus, anxiety, obesity, hyperlipidemia, non-alcoholic fatty liver disease, syndrome of obstructive sleep apnea, depression, sterility, and deficient vitamin D.[2]

Reproduction and Metabolism are basic and interdependent points of mammalian body physiology. Apposite metabolic homeostasis is pertinent for women's reproductive health. It is said that energy deficiency and a hyper-caloric environment that results in obesity are linked with reduced fertility chances. However, the intricacy of the phenomenon linking reproduction and metabolism is yet to be fully understood.[3, 4] Several hormonal metabolic signalling pathways affect women's

reproduction system. All these hormones affect women's reproductive system in varying capacities depending upon age sex and pubertal stage of growth. The gut hormone Glucagon-like peptide-1 deserves to be noticed because of substantial biochemical evidential support for the role and activity of GLP-1 in women's reproduction. Furthermore, GLP-1 receptor agonists (GLP-1 RA's) being capable of reducing glucose and weight are said to play a significant role in the management of type 2 DM and obesity.[5,6]

GLP-1 was recognized as a sequence of genes encoding the pre-proglucagon (Gcg) gene. It mediates its action through a GPCR (G-protein-coupled receptor, GLP-1R) that is found in many tissues, with the highest display seen in the lungs, pancreas and relatively less found in the Gastric cells, intestinal cells, kidneys, brain, and heart. Some recent research showed a sizeable number of GLP-1 receptors in women's reproductive system.[7, 8]

GLP-1 is considered to be involved in modulating the functions of hypothalamic GnRH neurons in the brain. GLP-1 causes a rise in LH concentration in serum with GnRH release being thought as a main phenomenon to induce LH hormone secretion from the pituitary gland.[9] It is observed that GLP-1 agonists in vivo boost LH hormone release. [10] The Luteinizing hormone is a glycoprotein hormone that is simultaneously released along with FSH (follicle/stimulating hormone) by the gonadotrophin cells in the anterior pituitary (adenohypophysis). Luteinizing hormone (LH) is an essential component of the neuron's signalling pathway comprising of the trio that is the hypothalamus, pituitary gland, and gonads. In this signalling pathway, the hormone LH secretion is boosted by GnRH (gonadotropin-releasing hormone) and reduced by the hormone estrogen in women and reproductive hormone testosterone in men. The luteinizing hormone has different functions, in both men and women. In both genders, this hormone LH is involved in primordial germ cell maturation and growth. The Luteinizing Hormone stimulated the testes Leydig cells to produce the hormone testosterone in males. In females, the luteinizing hormone boosts the production of steroidal hormones through the ovaries. Moreover, the LH plays a role to modulate and regulate the menstrual cycle in terms of duration in women through timely ovulation and egg implantation inside the uterus.[11]

The ovarian theca cells and granulosa cells not only produce steroid hormones but also produce important components that decide the biochemical features of follicular fluid (FF). The follicular fluid wraps the oocyte and plays a significant role in improving the quality of the oocyte thereby potentiating chances of fertility. This follicular fluid also plays a role in embryonic development. The Glucagon-like peptide-1 (GLP-1) was labelled as one of the constituents of Follicular fluid in humans during various research studies. It is seen that levels of hormones GLP-1 and others like leptin, insulin, C peptide, glucagon, and amino acids (branched chain) were increased in follicular fluid of obese women as compared to controls of normal weight.[12,13]

The study aimed to evaluate GLP-1 levels in PCOS females with DM and compare the results with the control group as GLP-1 receptor agonists are suggested to improve insulin sensitivity, reduce insulin resistance, and help in weight loss in obese PCOS diabetic women.

2. Materials & Methods

The current study was conducted in Tehsil Headquarters Hospital, Kalabagh, Tehsil Isakhel Mianwali between 15th September 2023 to 15th March 2024. This study included 52 patients with PCOS having DM and 52 age and weight-matched healthy females. The first group comprised 52 patients in the age group 18-30 years, diagnosed as having PCOS on ultrasound and biochemistry testing, based on Rotterdam criteria, by a specialist gynaecologist. The Second group included 52 healthy females included in this study also had an age range of 18-30 years with no symptoms/signs of hormonal dysfunction or PCOS. The consent was taken from all women included in the study. The blood fasting sugar levels and Glucagon-like peptide-1 levels were measured on Hitachi's fully automatic chemical analyzer. The age of menarche was also noted through a questionnaire. The data was assessed and analyzed by using IBM SPSS (Statistical Package for Social Sciences), version 23.

The descriptive results were noted as mean ± SD (standard deviation) in our study. The means of variables were compared by using an independent samples t-test. P value < 0.05 was considered a significant statistical value.

3. Results

Our study was comprised of 104 subjects. The patients were divided into two groups. The first group included 52 females diagnosed with PCOS having DM by a specialist gynaecologist and the second group included

52 healthy females. The details of the data and their distribution are given in Tables 1 and 2.

The mean ± SD of age in healthy women was 22.00±5.04 and the Mean ± SD of age in PCOS with DM was 22.57± 4.60 years. This difference in age in our study was non-significant (p=0.75) (Table 1). Mean ± SD of the weight of healthy females was 62.31±11.64 kg and Mean ± SD of weight in PCOS having DM was 64.12±16.29 Kg. This difference in weight in our study was also non-significant (p=0.12) (Table 1). The mean ± SD of menarche in healthy control women was 13.21±1.29 and the mean ± SD of PCOS with DM was 13.25±1.35. The difference in age of menarche in women of both groups was non-significant (p= 0.78) (Table 1).

Table 1: Comparison of Physical parameters between DM Women with PCOS and Healthy Women

Sr. No.	Parameter	Healthy Women (n=52)	Women with PCOS and DM (n=52)	*p*-value
		Mean ± SD	Mean ± SD	
1	Age (Years)	22.00±5.04	22.57±4.60	0.75
2	Weight (Kg)	62.31±11.64	64.12±16.29	0.120
3	Menarche Age (years)	13.21±1.29	13.25±1.35	0.78

**p-value < 0.05 is considered statistically significant. PCOS=polycystic ovarian syndrome, DM=Diabetes Mellitus.*

The mean ± SD of Blood Sugar Fasting in Healthy control women was 99.92 ± 4.46mg/dl and the mean ± SD of Blood Sugar Fasting in PCOS diabetes was 150.19 ± 30.20mg/dl. The difference in Blood Sugar fasting between the two groups was significant (p= 001*)(Table 2). The mean ± SD of Glucagon-like peptide-1 levels in healthy women was 0.41± 0.04ng/dl and the mean ± SD of Glucagon-like peptide-1 levels in PCOS with DM was 0.18± 0.03ng/dl. The difference in Glucagon-like peptide-1 levels between the two groups was significant (p= 001*) (Table 2).

Table 2: Comparison of Biochemical parameters between DM Women with PCOS and Healthy Women

	Parameter	Healthy Women (n=52)	Women with PCOS and DM (n=52)	*p*-value
		Mean ± SD	Mean ± SD	
1	Blood Sugar Fasting (mg/dl)	99.92 ± 4.46	150.19 ± 30.20	.001*
2	Glucagon-like peptide-1 (ng/dl)	0.41± 0.04	0.18± 0.03	.001*

**p-value < 0.05 is considered statistically significant. PCOS=polycystic ovarian syndrome, DM=Diabetes Mellitus*

4. Discussion

Polycystic ovarian syndrome (PCOS) is a very common endocrine disorder among women of reproductive age. The syndrome is very heterogeneous in terms of nature characterized by a combination of signs/symptoms of excess of androgens and ovarian dysfunction.[14]

The Glucagon-like peptide-1 secreted from intestinal entero-endocrine cells modulates meal-associated glycemic deviations through a boost of insulin release and reducing of secretion of glucagon. Moreover, recent studies have shown that GLP-1 receptor agonist treatment pharmacologically increases the availability of plasma GLP-1 to significant levels. Weight loss and abdominal fat reduction in patients with type 2 DM or obese and prediabetes women have been made possible by using GLP-1 receptor agonists in various novel studies. These receptor agonists' beneficial effects in PCOS through possible involvement in the hypothalamic-pituitary-gonadal axis is an area of active research. [15, 16]

Our study showed that novel gut markers such as Glucagon-like peptide-1 levels are significantly lower in patients with PCOS having DM as compared to healthy women. These results are consistent with the study done by Aljoda et al. [17]

In another study done by Ferjan et al, low levels of Glucagon-like peptide 1 were seen in patients with PCOS having prediabetes phase which is in agreement with our study. [18]

The GLP-1 receptors' anatomical placement throughout women's reproductive system and the effects of GLP-1 in clinical studies indicate that it may be an important linking pathway between the metabolic and reproductive systems. The stimulation of GLP-1 and its mimetic in mammal reproduction displays effects beyond only weight reduction. It is also observed that the GLP-1 hormone seems to have anti-fibrotic and anti-inflammatory impressions in gonads and the endometrial lining affected by DM and PCOS. [19]

Another study done by Aydin et al revealed that GLP-1 levels are reduced in PCOS as compared to healthy controls which is in agreement with our findings.[20] The various studies through their experimental research evidence indicate that low GLP-1 levels are involved in ovarian dysfunction leading to problems in steroidogenesis and follicles formation in PCOS.[21]

The GLP-1 and GLP-1 receptor agonists play a critical contribution in reproduction in mammals and it may be

considered as a novel metabolic link for the reproductive system that leads to various effects including weight loss in women.[22]

In another in vivo experimental study, the acute treatment with GLP-1 receptor agonists in female rats resulted in elevated pre-ovulatory LH levels indicating a strong association of GLP-1 with GnRH.[23]

In recent studies Glucagon-like peptide/1 receptor agonists (GLP-1RA) have been tested and recommended for PCOS and obese diabetic women as these pharmacological agents are involved in improving insulin sensitivity, reducing insulin resistance and helping in weight loss, and also improving non-alcoholic fatty liver problems.[24]

In recent advancements, some anti-diabetics such as Liraglutide (a glucagon-like peptide-1 receptor agonist) are said to be involved positively in weight and abdominal fat loss, in obese individuals, prediabetics, and type 2 DM patients. A large number of clinical evidential studies have described that treatment with liraglutide helped achieve considerable body weight, body mass index (BMI), and abdominal girth reduction in obese and overweight females having PCOS. [25] In some other recent research, Exenatide, another glucagon-like peptide-1 receptor agonist, is declared effective in reducing weight and insulin resistance in patients with DM as well as PCOS. [26]

5. Conclusion

Low plasma Glucagon-like peptide-1 levels are seen in PCOS patients having DM as compared to healthy Controls.

INSTITUTIONAL REVIEW BOARD

00291116MMANA Dated 30-11-2016

CONFLICTS OF INTEREST- None

Financial support: None to report.
Potential competing interests: None to report

Contributions:

M.M - Conception of study
M.M - Experimentation/Study Conduction
M.M, R.N.K - Analysis/Interpretation/Discussion
S.B.A, A.S - Manuscript Writing
R.N.K, S.B.A, M.L - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

References

1. Islam H, Masud J, Islam YN, Haque FKM. An update on polycystic ovary syndrome: A review of the current state of knowledge in the diagnosis, genetic etiology, and emerging treatment options. *Women's Health*. 2022; 18. Doi: 10.1177/17455057221117966.
2. Shrivastava S, Conigliaro RL. Polycystic Ovarian Syndrome. Med Clin North Am. 2023 Mar;107(2):227-234. doi: 10.1016/j.mcna.2022.10.004. Epub 2022 Dec 26. PMID: 36759093.
3. Izzi-Engbeaya C, Comninos AN, Clarke SA, Jomard A, Yang L, Jones S, et al. The effects of kisspeptin on β-cell function, serum metabolites and appetite in humans. Diabetes Obes Metab. 2018 Dec; 20(12):2800-2810. doi: 10.1111/dom.13460. Epub 2018 Aug 16. PMID: 29974637; PMCID: PMC6282711.
4. Silvestris E, de Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. Reprod Biol Endocrinol. 2018 Mar 9;16(1):22. doi: 10.1186/s12958-018-0336-z. PMID: 29523133; PMCID: PMC5845358.
5. Comninos AN, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. Hum Reprod Update. 2014 Mar-Apr;20(2):153-74. doi: 10.1093/humupd/dmt033. Epub 2013 Oct 30. PMID: 24173881.
6. Lamos EM, Malek R, Davis SN. GLP-1 receptor agonists in the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol. 2017 Apr;10(4):401-408. doi: https://doi.org/10.1080/17512433.2017.1292125
7. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes Obes Metab. 2018 Feb;20 Suppl 1:5-21. doi: 10.1111/dom.13129. PMID: 29364588.
8. Nishiyama Y, Hasegawa T, Fujita S, Iwata N, Nagao S, Hosoya T, et al. Incretins modulate progesterone biosynthesis by regulating bone morphogenetic protein activity in rat granulosa cells. J Steroid Biochem Mol Biol. 2018 Apr;178:82-88. doi: 10.1016/j.jsbmb.2017.11.004. Epub 2017 Nov 9. PMID: 29129645.
9. Heppner KM, Baquero AF, Bennett CM, Sarah R, Kirigiti MA, Bennet B et al. Glp-1r signaling directly activates arcuate nucleus kisspeptin action in brain slices but does not rescue luteinizing hormone inhibition in ovariectomized mice during negative energy balance. *Eneuro*. 2017. doi:10.1523/ENEURO.0198-16.2016
10. Simpson EM, Clarke IJ, Scott CJ, Stephen CP, Rao A, Gunn AJ. The GLP-1 agonist, exendin-4, stimulates LH secretion in female sheep. J Endocrinol. 2023 Aug 17;259(1):e230105. doi: 10.1530/JOE-23-0105. PMID: 37466202; PMCID: PMC10448581.
11. Nedresky D, Singh G. Physiology, Luteinizing Hormone. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539692/
12. Bou Nemer L Shi H Carr BR Word RA Bukulmez O. Effect of body weight on metabolic hormones and fatty acid metabolism in follicular fluid of women undergoing in vitro fertilization: a pilot study. *Reproductive sciences (thousand oaks calif)*. 2019:404-411. doi:10.1177/1933719118776787
13. Sun Z, Li P, Wang X, Lai S, Qiu H, Chen Z et al. GLP-1/GLP-1R Signaling Regulates Ovarian PCOS-Associated Granulosa Cells Proliferation and Antiapoptosis by Modification of

Forkhead Box Protein O1 Phosphorylation Sites. Int J Endocrinol. 2020 Jun 19;2020:1484321. doi: 10.1155/2020/1484321. PMID: 32655632; PMCID: PMC7321515.

14. Zehravi M, Maqbool M, Ara I. Polycystic ovary syndrome and infertility: an update. Int J Adolesc Med Health. 2021;34:1–9.
15. Muller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019; 30:72–130.
16. Brown E, Cuthbertson DJ, Wilding JP. Newer GLP-1 receptor agonists and obesity-diabetes. Peptides. 2018; 100:61–7.
17. *Aljoda, BM, Shfeeq, NK, Raed A, Abdulhameed. Novel Biomarker in Polycystic ovary syndrome (PCOS) infertile females with Diabetes Mellitus prone to atherosclerosis. 2016.*
18. Ferjan S, Jensterle M, Oblak T, et al. An impaired glucagon-like peptide-1 response is associated with prediabetes in polycystic ovary syndrome with obesity. *Journal of International Medical Research*. 2019;47(10):4691-4700. doi:10.1177/0300060519865351
19. Jensterle M, Janez A, Fliers E, DeVries JH, Vrtacnik-Bokal E, Siegelaar SE. The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective. https://doi.org/10.1093/humupd/dmz019
20. Aydin K, Arusoglu G, Koksal G, Cinar N, Aksoy DY, Yildiz BO. Fasting and post-prandial glucagon like peptide 1 and oral contraception in polycystic ovary syndrome. Clin Endocrinol (Oxf). 2014 Oct;81(4):588-92. doi: 10.1111/cen.12468. Epub 2014 May 19. PMID: 24730585.
21. Franks S, Stark J, Hardy K (2008) Follicle dynamics and anovulation in polycystic ovary syndrome. Hum Reprod Updat 14(4):367–378. https://doi.org/10.1093/humupd/dmn015
22. Andersen A, Lund A, Knop FK, Vilsboll T (2018) Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol 14(7):390–403. https://doi.org/10.1038/s41574-018-0016-2
23. Outeirino-Iglesias V, Romani-Perez M, Gonzalez-Matias LC, Vigo E, Mallo F (2015) GLP-1 increases preovulatory LH source and the number of mature follicles, as well as synchronizing the onset of puberty in female rats. Endocrinology 156(11):4226–4237. https://doi.org/10.1210/en.2014-1978
24. Siamashvili M, Davis SN. Update on the effects of GLP-1 receptor agonists for the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol. 2021 Sep;14(9):1081-1089. doi: 10.1080/17512433.2021.1933433. Epub 2021 May 27. PMID: 34015974.
25. Papaetis GS, Filippou PK, Constantinidou KG, Stylianou CS. Liraglutide: New Perspectives for the Treatment of Polycystic Ovary Syndrome. Clin Drug Investig. 2020 Aug;40(8):695-713. doi: 10.1007/s40261-020-00942-2. PMID: 32583294.
26. Ma RL, Deng Y, Wang YF, Zhu SY, Ding XS, Sun AJ. Short-term combined treatment with exenatide and metformin for overweight/obese women with polycystic ovary syndrome. Chin Med J (Engl). 2021 Nov 3;134(23):2882-2889. doi: 10.1097/CM9.0000000000001712. PMID: 34732660; PMCID: PMC8667970.