Original Research Article

Role of Ghrelin and Adiponectin among Type 2 Diabetes mellitus patients attended at Tertiary care teaching hospital

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Abstract

Introduction: Diabetes mellitus (DM) refers to a bunch of disorders of metabolism that share the phenotypic sign of hyperglycaemia. Different variants of DM are caused due to the interaction of various genetic factors with environmental factors. **Methods:** overall total number of 50 patients with type 2 DM, aged from 20-60 years attending OPD of a tertiary hospital was taken into study, whose blood glucose level before meals was [≥ 120 mg/dl] and after meals was [≥ 140 mg/dl], taking oral hypoglycaemic medicines only and not taking insulin therapy was included in the examination. **Result** Overall, 50 patients of age group from 20-60 years were taken in the examination. among which type 2 DM was more predominant in the employed group from 51-60 years (48%) thereby 41-50 years (34%). It was seen that 52% of patient of type-II diabetes mellitus had history of same complaint in the family. From the research, polyuria (52%) and polydipsia (48%) were the commonest symptoms seen in the patients suffering from DM. According to the drug therapy recommendations, Biguanides (92.1%) and Sulfonylurea (87.2%) were the commonest prescribed oral hypoglycaemic medicines amongst entire oral hypoglycaemic group of medicines, followed by thiazolidinediones (19.2%), Dipeptidyl peptidase-4 inhibitors (16%), α-glucosidase inhibitor (3.2%) and meglitinides (1.9%) individually. **Conclusion:** The increasing pattern of inactive daily life routine and more occurrence of overweight has put up enhancement in the individuals of diabetes, which contributes to enormous requirement of hypoglycemic drugs and motivating corporations to spend much on research and development for producing targeted formulae.

Key words: Hyperglycemia, Polyurea, Polydipsia, Hypoglycaemic.

Introduction

Diabetes mellitus (DM) refers to brunch of disorders of metabolism that share the phenotypic sign of hyperglycaemia. Different variants of DM are caused due to the interaction of various genetic factors with environmental factors. It is a chronic illness, influencing approximately six percent of the world populace. It is linked with irregular carbohydrate, protein and lipid digestion[1]. The treatment of type-1 diabetes relies on insulin mostly, while the treatment of type-2 diabetes is mostly treated with oral hypoglycaemic agents (OHAs). Diabetes, if not controlled, caused numerous acute and chronic difficulties[2].

The Chronic difficulties of diabetes make it essential to suggest medicines for these individuals for lifetime. Furthermore, many of diabetes individuals succumb to circulatory illness like increased blood pressure, hyperlipidaemia and ischaemic heart disease[3]. This additionally requires multi drugs in these individuals. Numerous difficulties are seen by the use of these medicines. This comprises the use of illogical mixtures of drugs, more prescription of drugs like anti infectious and supplements[4].

Frequently, the chronically diseased individually such as diabetic patients suffers from several illnesses and therefore are suggested to use several medicines. Furthermore, illogical suggesting can cause more cost for treatment, which can cause inconstancy. Research from the United State of America stated that around 1.29 million individuals with debilities do not take drugs as suggested due to high cost and due to which half of them seen with other health issues[5]. In diabetes, the difficulties can be prohibited only if the patient keeps frim glycaemic regulation.

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Achieving a drug usage examination can give valued data to the scientists, strategy producers and the medicine and therapeutics board associates to regulate the design of medicine usage[6].

Ghrelin is an acylated, 28-amino-acid peptide that promotesthe release of GH in the hypothalamus. It is the naturalligand of the GHSR-1a receptor[7]. It was found that ghrelin is then only peripheral hormone which stimulates food intake by acting in hypothalamus and is involved in multiple endocrine and non-endocrine processes such regulation of glucose metabolism and insulin secretion[8]. Insulin is shown to inhibit ghrelin secretion in healthy normal-weight and overweight persons, and both oral and intravenous glucose loads are also shown to regulate ghrelin secretion in humans[9] Physiological increases in insulin levels may play a key role in regulating postprandial plasma ghrelin concentrations, since meal-induced ghrelin suppression is absent in severe insulin deficiency[10]. An increase in insulin after the oral or intravenous glucose administration could contribute to the inhibitory effect of glucose on ghrelin concentrations[11]

Adiponectin, a hormone secreted from fat cells, has insulin-sensitizing and anti-inflammatory properties. Low adiponectin plasma levels are associated with the insulin resistance that manifests in obesity and diabetes mellitus, both of which are risk factors for pancreatic cancer[12]. Adiponectin effects are mediated by adiponectin receptors, which occur as two isoforms (AdipoR1 and AdipoR2). Adiponectin has direct actions in liver, skeletal muscle, and the vasculature. Adiponectin exists in the circulation as varying molecular weight forms, produced by multimerization[13]. Several endoplasmic reticulum ER-associated proteins, including ER oxidoreductase 1-α (Ero1-α), ER resident protein 44 (ERp44), disulfide-bond A oxidoreductase-like protein (DsbA-L), and glucose-regulated protein 94 (GPR94), have recently been found to be involved in the assembly and secretion of higher-order adiponectin complexes[14].

Methods

This is a prospective and observational study conducted at Tertiary care teaching centre over a period of 1 year. Overall total number of 50 patients with type 2 DM, aged from 29-71 years attending OPD of a tertiary hospital was taken into study, whose blood glucose level before meals was [≥ 120 mg/dl] and after meals was [≥ 140 mg/dl], taking oral hypoglycaemic medicines only and not taking insulin therapy was included in the examination.

Individuals with type 1 DM with other illnesses such as high blood pressure, cardiac and circulatory problems, renal problems, gestation, cigarette smoker were not included in the examination.

Initially, patient's vocal agreement was taken. Later, details of age, family details and history, present signs such as polyuria, polyphagia and polydipsia were collected and filled in the form.

Formerly, fasting and post lunch glucose level of blood was collected from the hospital data.

Based on the patient's situation, the doctors had divided the drugs into monotherapy (Glimepiride, metformin, Pioglitazone, Voglibose, Telnigliptine), dual therapy [sulphonylurea (Glimepiride) and metformin] and triple therapy [sulphonylurea (Glimepiride), metformin and thiazolidinediones (Pioglitazone)]. Patients who were included in the study was asked to come after a week for re-examination.

During the next visit, fasting and post lunch blood samples were taken and sent to laboratory for tests. All the patients who were included in the study was supervised firmly with regards to diet regime and physical exercise and were instructed to follow diabetic diet regime of WHO.

The level of Adiponectin was assayed using Assaymaxhuman adiponection ELISA (sandwich) kit for research purpose. The quality control samples were supplied along with kit by manufacturer processed during analysis.

Statistical Analysis

Complete information gathered was coded and kept in the system for transformation and evaluation, utilizing MS-Excel and SPSS 25th for windows. Later percentage was carried out.

Results

Overall, 50 patients of age group from 20-60 years were taken in the examination. among which type 2 DM was more predominant in the employed group from 51-60 years (48%) thereby 41-50 years (34%) in table 1.

Table 1: Occurrence of type 2 DM in several age groups

Age Group	Frequency (n= 50)	Percentage
20-30	2	4.0%
31-40	7	14%
41-50	17	34%
51-60	24	48%

Table 2: Type-II diabetes mellitus had history of same complaint in the family

DM-II	Frequency	Percentage
Family history	26	52
Non-family history	24	48
Total	50	100

It was seen that 52% of patient of type-II diabetes mellitus had history of same complaint in the family in table 2.

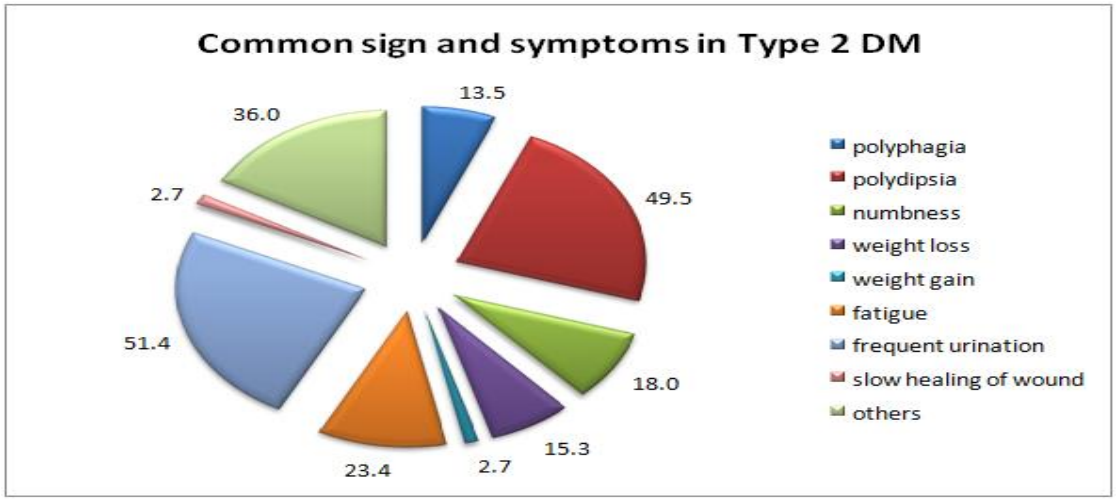

Fig. 1: Common Sign and symptoms of Type II DM

From the research, polyuria (51.4%) and polydipsia (49.5%) were the commonest symptoms seen in the patients suffering from DM in figure 1.

Table 3: Practice of prescribing oral antidiabetic drug in Type II DM

Group	Frequency	Percentage
Sulfonylurea	43	87.2
Biguanides	46	92.1
Thiazolidinediones	10	19.2
Dipeptidyl peptidase-4 inhibitors	8	16.0
α - glucosidase inhibitor	2	3.2
Meglitinides	1	1.9

According to the drug therapy recommendations, Biguanides (92.1%) and Sulfonylurea (87.2%) were the commonest prescribed oral hypoglycaemic medicines amongst entire oral hypoglycaemic group of medicines, followed by thiazolidinediones (19.2%), Dipeptidyl peptidase-4 inhibitors (16%), α-glucosidase inhibitor (3.2%) and meglitinides (1.9%) individually in table 3.

Table 4: Change in blood Glucose level and other parameters

Drug	Change in blood Glucose (%)		Change of HbA1c (%)	Change in Ghrelin (ng/L)	Change in Adiponectin(mg/ml)	No. of subject
Drug	Pre-prandial	Post prandial				
Biguanides	18.1	22.0	0.9	121.7±16.9	11.68±2.53	4
Sulphonylureas	14.9	38.9	1.2	109.3±11.3	13.42±3.74	2
Sulphonylureas + metformin	27.1	31.1	1.7	83.4±8.6	17.25±5.43	23
Sulphonylureas + metformin + thiazolidinediones	26.9	33.1	1.9	73.8±6.3	23.12±7.02	21

Reductions are the average percentage **change** in blood glucose

The dual drug therapy [sulphonylureas and biguanides] were observed to be decreased by 27.1 % and 31.1 % individually in fasting and in post lunch blood glucose. Triple drug therapy [sulphonylurea, thiazolidinediones and biguanides] in fasting and in post lunch blood glucose 26.9 % and 33.1 % respectively. Change of HbA1c were 0.9% to 1.9% from single drug therapy to Triple drug therapy. Change of Ghrelin level from 121.7±16.9 to 73.8±6.3 ng/L from single to Triple drug therapy. Serum Adiponectin level were 11.68±2.53 mg/ml during Biguanides usage and during Triple drug therapy were 23.12±7.02 mg/ml in Table 4

Discussion

From the research, it was observed that type 2 DM was predominant between 51-60 years (48%) thereby 41-50 years (34%). The dominance of DM from 39-51 years of age was about 26%. Hereditary aspect is also an influencing issue of Non-Insulin Dependent Diabetes Mellitus due to monogenic imperfections in beta-cell working, which is generally defined as the early onset of hyperglycaemia in the young age (usually under 24 years). In this examination, it was seen that 52.1%of individuals suffering from type 2 DM had the similar complaint in other family members.

In our study, polyuria (52%) and polydipsia (48%) were the commonest symptoms seen in the patients suffering from Diabetes. Our test outcomes were almost same with that of the study done by McCulloch which proposed that the chief complaints are polydipsia, polyuria and polyphagia[15]. These indications are seen as result of diabetes. If the glucose level in blood is much high, it is not properly reabsorbed by the renal tubule of the nephrons in the kidneys, therefore it increases the glucose level in urine (glycosuria) thereby increasing the osmotic pressure[16]. This does not allow the kidneys to reabsorb water properly, hence produces more urine (frequency of micturition)[17].

From our examination, Biguanides (92.1%) and Sulfonylurea (87.2%) were the commonest prescribed oral hypoglycaemic medicines amongst entire oral hypoglycaemic group of medicines, followed by thiazolidinediones (19.2%), Dipeptidyl peptidase-4 inhibitors (16%), α-glucosidase inhibitor (3.2%) and meglitinides (1.9%) individually. This obeys with the research carried out by Stumvoll M et al[18]. Biguanides has the probable benefit of pointing insulin resistance, instead of enhancing the plasma concentration of insulin which is the initial feature of the diabetes. That is why it is the commonest prescribed oral hypoglycaemic medicine. Moreover, biguanides does not increase body weight and may decrease fat tissue in the body. Therefore, they can be chosen in over weighted and normal people with insulin resistance[19].

As per the published works, biguanides causes low hypoglycaemia than sulphonylureas[20]. In addition, sulfonylureas leads to increase in the body weight and persuade much hypoglycemia. Hence it is seen that biguanide has got more benefits than sulphonylurea.

In our study, it is observed that the commonest medicines from sulphonylurea group are glimepiride (77.5%) thereby glicazide (6.3%) and glibenclamide (1.8%) individually. Our results are same as of those study carried out by RK campbell[21]. In his research, glimepiride, sulphonylurea which is pharmacologically different from other sulphonylureas due to their receptor binding features and firmly varied reaction on ATP sensitive K+ channels. channels[22].

The pharmacokinetic effect of glimepiride makes it apt for regular dosage of once in a day, with a good option for the patients having type 2 DM, whose glucose levels are not controlled with diet and physical exercise solely and for those who wants to get good diabetic control[23]. Various mixtures of oral hypoglycaemic drugs such as sulfonylurea and metformin, a sulfonylurea and an alpha glucosidase inhibitor (Voglibose); a sulfonylurea, metformin and a thiazolidinedione have shown much improved glucose control in contrast to monotherapy.

Thiazolidinediones, sulfonylureas, and metformin shown alike decreased in Ghrelin levels when used as Triple therapy. Mixed therapies had additional outcomes, creating a complete decrease in Ghrelin levels more than monotherapy. A similar association of low levels of ghrelin with T2DM was reported among Finnish participants in the Oulu Project Elucidating Risk of Atherosclerosis study. This is probably because high ghrelin levels decrease total body fat, and consequently increase the expression of insulin receptors in adipose tissue[24].

The double drug therapy of sulphonylureas + biguanides and triple drug therapies of sulphonylurea, thiazolidinediones and biguanides were observed to decrease fasting glucose levels by 26.5% and 27.1 % individually and post lunch glucose levels by 31.1 % and 33.1 % individually. This outcome is also similar to the results seen in the research done by Qaseem A et al in 2007[25]. In his research, it is observed that both the dual and triple drug therapies decrease the blood glucose level to similar extent. Metformin was much effective when compared to other drugs as monotherapy even when prescribed with other combination drug therapy for decreasing blood glucose amount[26].

Anyhow, this outcome is against the research done by Roberts VL et al, in which it is seen that the patients with type 2 DM were not effectively controlled by dual drug therapy of metformin and thiazolidinedione , the additional use of glimepiride has shown the good results along in glycaemic control in contrast with placebo with a satisfactory acceptability profile[27].

The influence of ghrelin on the regulation of glucose homeostasis was first hypothesized following the observation of a negative correlation between circulating ghrelin and insulin levels in humans[28]. Later, an association between ghrelin and the homeostasis model of assessment, an index of insulin resistance, further supported the involvement of ghrelin in the development of insulin resistance and type 2 diabetes[29]. Subsequently, the association of ghrelin with insulin, glucose and insulin resistance indexes was investigated in different populations with definite metabolic profiles. For instance, in obese and non-obese children and obese adults with or without insulin resistance or type 2 diabetes, pre-meal total ghrelin levels were inversely associated to insulin levels and the severity of insulin resistance[30, 31].

Adiponectin is a fat-derived hormone that appears to play a crucial role in protecting against insulin resistance/diabetes and atherosclerosis. Decreased adiponectin levels are thought to play a central role in the development of type 2 diabetes, obesity and cardiovascular disease in humans. Research in humans and rodent models has consistently demonstrated the role of adiponectin as an important physiological regulator of insulin sensitivity, glucose, and lipid metabolism as well as cardiovascular homeostasis[32].

Conclusion

The increasing pattern of inactive daily life routine and more occurrence of overweight has put up enhancement in the individuals of diabetes, which contributes to enormous requirement of hypoglycemic drugs and motivating corporations to spend much on research and development for producing targeted formulae. Our research has shown that dual drug therapy (sulphonylurea and biguanide) and triple drug therapy (sulphonylurea, thiazolidinedione and biguanide) showed an improve of fasting, post lunch blood glucose levels, HbA1c, Ghrelin and Adiponectin level.

References

1. R. Khursheed, S. Singh, S. Wadhwa, B. Kapoor, M. Gulati, R. Kumar, et al., Treatment strategies against diabetes: Success so far and challenges ahead, Eur. J. Pharmacol. 2019;862:172625.
2. S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030, Diabetes. Care 2004;27: 1047–1053.
3. C. Wong, H. Al-Salami, C. Dass, Potential of insulin nanoparticle formulations for oral delivery and diabetes treatment, J. Control. Release 2017;264:247–275.
4. A.Chaudhury, C. Duvoor, V.S.R. Dendi, S. Kraleti, A. Chada, R. Ravilla, et al., Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management, Front. Endocrinol. 2017;8: 1–12.
5. R. Feingold, et al., in: K.R. Feingold, B. Anawalt, A. Boyce (Eds.), Oral and Injectable (Non-insulin) Pharmacological Agents for Type 2 Diabetes, MDText. com, Inc., South Dartmouth (MA), 2000. Endotext
6. S. Tan, J. Mei Wong, Y. Sim, S. Wong, S. Mohamed Elhassan, S. Tan, et al., Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention, Diabetes. Metab. Syndr. 2019;13: 364–372.
7. Amir, Q., Linda, L., Sweet, D. E., Starkey, M., & Shekelle, P. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline from the American College of Physicians. Ann Intern Med, 2012;156:219-31.
8. Bays, H., Chapman, R., & Grandy, S. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: Comparison of data from two national surveys. Int J Clin Pract , 2007;61(5):737-47.
9. Bennett, Maruthur, Singh, Segal, Wilson, & R, C.Comparative effectiveness and safety of medications for type 2 diabetes: Anupdate including new drugs and 2-drug combinations. Ann Intern Med, 2011;154:602-13.
10. Bolen, S., Feldman, L., Vassy, J., Wilson, L., & al, H.-C. Y. Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. Ann of Internal Medicine, 2007;147 (6): 386-399.
11. Campbell, R., & Glimepiride. Role of a new sulfonylurea in the treatment of type 2 diabetes mellitus. Ann Pharmacother , 1998;32 (10):1044-52.
12. Cheng, & IG, F. (2005). Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ , 172, 213-26.
13. Mishra L (ed). Drug today: Ready reckoner of current medical formulations. Lorina Publications (India) Inc. New Delhi. Oct-Dec 2015.
14. Current index of medical specialities. UBM Medica India Private Limited. 2016; 132:479-87.
15. Agarwal AA, Jadhav PR, Deshmukh YA. Prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients. J Basic Clin Pharma. 2014; 5:79-83.
16. Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006;116:1802-1812.
17. Grundy SM. Atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance. Clin Cornerstone 2006;8(Suppl 1):S21-S27.
18. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol 2006;47:1093-1100.
19. Hunter SJ, Garvey WT. Insulin action and insulin resistance: diseases involving defects in insulin receptors, signal transduction, and the glucose transport effector system. Am J Med 1998;105:331-345.
20. Stannard SR, Johnson NA. Insulin resistance and elevated triglyceride in muscle: more important for survival than "thrifty" genes? J Physiol 2004;554:595-607.
21. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-946.
22. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm 2013;2013:139239
23. Dezaki K, Sone H, Yada T. Ghrelin is a physiological regulator of insulin release in pancreatic islets and glucose homeostasis. Pharmacol Ther 2008;118:239-249.
24. Yada T, Dezaki K, Sone H, Koizumi M, Damdindorj B, Nakata M, et al. Ghrelin regulates insulin release and glycemia: physiological role and therapeutic potential. Curr Diabetes Rev 2008;4:18-23.
25. Ou HY, Wang CY, Yang YC, Chen MF, Chang CJ. The association between nonalcoholic fatty pancreas disease and diabetes. PLoS One. 2013;**8**:e62561.
26. Cersosimo E, Solis-Herrera C, Trautmann ME, Malloy J, Triplitt CL. Assessment of pancreatic β-cell function: review of methods and clinical applications. Curr Diabetes Rev. 2014;10(1):2–42.
27. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest. 1981;68:1456-1467.
28. Tschöp M, Wawarta R, Riepl RL, et al. Post-prandial decrease of circulating human ghrelin levels. Journal of Endocrinological Investigation. 2001;24(6):RC19–RC21.
29. English PJ, Ghatei MA, Malik IA, Bloom SR, Wilding JPH. Food fails to suppress ghrelin levels in obese humans. Journal of Clinical Endocrinology and Metabolism. 2002;87(6):2984–2987.
30. Higgins SC, Gueorguiev M, Korbonits M. Ghrelin, the peripheral hunger hormone. Annals of Medicine 2007; 39(2):116–136.
31. Ukkola O, Pöykkö SM, Kesäniemi YA. Low plasma ghrelin concentration is an indicator of the metabolic syndrome. Journal of Clinical Endocrinology & Metabolism. 2005;90:6448–6453.
32. Matsuda M., Shimomura I., Sata M., Arita Y., Nishida M., Maeda N., Kumada M., Okamoto Y., Nagaretani H., Nishizawa H. Role of adiponectin in preventing vascular stenosis the missing link of adipo-vascular axis. J. Biol. Chem. 2002; 277:37487–37491.

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