Research Article

The Correlation of Insulin Resistance with B cell Function, Metabolic, and Hormonal Parameters in Type 2 Diabetic Women Treated with Metformin

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ABSTRACT

Beta cell dysfunction and insulin resistance are believed to cause persistent hyperglycemia which characterizes type 2 diabetes. Previous study found potential relationship between elevated free testosterone level and an insulin resistance status in hyperprolactinemia women. Treatment with different doses of metformin result in a significant reduction in prolactin level. This study is designed to explore the potential role of metformin in improving β cell function via its effect on ameliorating metabolic and hormonal parameters in type 2 diabetic women by direct or indirect relationship. A 20 middle age newly diagnosed type II diabetes mellitus female patients treated with 1500mg metformin daily for 6 months. Fasting blood glucose, fasting serum insulin, HOMA-IR, HOMA-B, serum prolactin, total and free testosterone were measured. Following three to six months with metformin therapy, significant improvement in glycemic parameters, insulin resistance, β cell function was clear($P<0.05$). Similarly for endogenoustotal and free testosterone, and serum prolactin levels were significantly reduced ($P<0.05$). Fasting serum insulin positively correlated only with serum prolactin after 6 months of metformin therapy ($P<0.05$). Fasting serum insulin and IR showed negative correlation with free testosterone at the baseline and after metformin therapy ($P<0.05$). The reduction in serum prolactin and endogenous total and free testosterone following metformin therapy may potentially reduce fasting serum insulin, insulin resistance, and thereby improves β cell function.

Keywords: Type II diabetes mellitus, prolactin, testosterone, metformin, HOMA-IR, HOMA-B.

INTRODUCTION

Beta cell (β cell)dysfunction and insulin resistance are believed to cause persistent hyperglycemia which characterizes type 2 diabetes.[1] The two pathological states influence each other and synergistically exacerbate diabetes.[2] Preserving β cell function and insulin signaling in β cells and insulin signaling in the glucose recipient tissues will maintain glucose homeostasis.[3]

The interplay between beta cell dysfunction and insulin resistance remains complex process.[4] A decreases in β cell function were modeled by changing its response to plasma glucose concentrations, and the well-defined HOMA –B model. The latter is derived from a mathematical assessment of the interaction between βcell function and IR in an idealized model that is then compute the steady-state insulin and glucose concentrations.[5]

Pancreatic β cells are exposed during β cell compensation to metabolic changes associated with obesity. Factors commonly associated with obesity — such as insulin resistance (including that in β cells), adipokines, FFAs, reactive oxygen species, and endoplasmic reticulum–associated stress — should therefore be examined as candidates for inducers of β cell failure.[6]

Insulin resistance develop via the existence of intertissue communication mediated not only by hormones and the nervous system but also through bioactive molecules produced by several cell types.[7]

Effects of prolactin in type 2 diabetes mellitus and its complications shown in previous studies, existing experimental studies indicate an influence of prolactin on type 2 diabetes mellitus via its metabolic effects on adipose tissue [8,9], development and growth of pancreatic ß-cells[10,11], insulin resistance[9,12], and lipid metabolism.[13,14] The ability of prolactin to stimulate insulin [10] and suppress adiponectinin addition to interleukin-6 release further suggests an important role in the manifestation of insulin resistance.[8] In addition, high prolactin levels may increase proinflammatory response indicating an involvement in human immune dysfunction.[15, 16]

Previous study found potential relationship between elevated free testosterone level and an insulin resistance status in hyperprolactinemia women.[17] Moreover, previous study found that HOMA-IR had significant correlation with free testosterone in premenopausal T2DM women with high insulin level only, but no significant correlation with total testosterone and SHBG was found among all study patients with the high, low, or near normal fasting insulin level.[18]

Metformin improves insulin sensitivity in liver, muscle and fat. However, the functional roles of metformin action in pancreatic β cells remain unclear.[19] One study showed that Metformin improved HOMA-B more than other oral hypoglycemic agents.[20] Also, treatment with

different doses of metformin result in a significant reduction in prolactin level.[21]

Taking together these findings, this study is designed to explore the potential role of metformin in improving β cell function via its effect on ameliorating metabolic and hormonal parameters in type 2 diabetic women by direct or indirect relationship.

MATERIAL AND METHODS

The present study was a prospective, open label, randomized controlled group study. A 20 middle age newly diagnosed type II diabetes mellitus female patients were enrolled in the study in addition to 18 healthy females matched with patients for age were included. The local clinical research ethics committee in accordance with Helsinki declaration 1998, approved the study protocol and all subjects gave written informed consent to participate in the study.

The patients evaluated for inclusion/exclusion criteria. The inclusion criteria include newly diagnosed female with type II diabetes according to ADA diagnostic criteria.[16] The exclusion criteria include drugs and medical conditions that affect serum prolactin such as a medical history of prolactinema,hypothyroidism or drugs that increase prolactin level,pregnancy and breast feeding.

The patients were treated with 1500mg metformin daily for 6 months. Blood samples were obtained by venipuncture from a peripheral vein after 12hour fasting and prior to any treatment as baseline then after 3 and 6 months the blood was allowed to clot and serum was separated and stored at −20 °C.Fasting blood glucose (FBG) was measured by enzymatic colorimetric test using commercial kit (Bio lab reagent–France). Fasting serum insulin (FSI) was analyzed using commercial kit based on sandwich ELISA test (DRG-international Inc. USA).

Insulin resistance and B-cell function was determined by using homeostatic model assessment (HOMA) depending on fasting insulin concentration and fasting glucose concentration and calculated as [18]:

HOMA-IR = fasting insulin (microU/L) x fasting glucose (mmol/L)/22.5

HOMA-B% =20 × fasting insulin (microU/L) /fasting glucose (mmol/L)− 3.5

With the stored frozen samples, total and free testosterone levels were measured using ELISA kit (DRG-international Inc. USA).And the serum level of prolactin was measured by a commercial ELISA kit.

Statistical Analysis

Data were expressed as mean± SD. statistics were performed using SPSS (version 16). Comparison between pre and post treatment results in patients group was assessed by using Paired sample t-test.ANOVA was used to assess differences between groups (patients and control).

Correlation among variables was performed using Pearson's correlation coefficient. A p-value of <0.05 was considered significantly different.

RESULTS

Changes in glycemic parameters, β cell function, insulin resistance, and endogenous hormones

Table 1summarizes the metabolic and hormonal parameters of the 20 middle-aged premenopausal women enrolled in this prospective study.

The BMI in T2DM women tended to be comparable to control non diabetic subjects at the baseline level (28.37±0.16 vs 28.34±0.13 kg/m^2)

Fasting blood glucose was significantly higher among patient group (13.03 ± 0.74 mmol/L) compared to controls (4.57 ±0.33mmol/L) (P<0.05) at the pre-treatment level. Significant reduction in FBG was found after 3 and 6 months with 1500mg/day metformin (10.18 ± 1.15 mmol/L) and (7.6944 ± 1.06 mmol/L) (P<0.01) respectively.

Fasting serum insulin tended to be comparable between patient group and control non diabetic subjects at the pre-treatment level (9.63 ± 0.44 vs 9.28 ± 0.88 mU/ml) respectively. Significant reduction in FSI was found 6 months with 1500mg/day metformin (8.85 ± 0.42 mU/ml) (P<0.05) compared to pre-treatment level.

HOMA-IR score was significantly high among patient group (5.56 ± 0.40) compared to the control subjects (1.88 ± 0.22)(P<0.05) at the pre-treatment level. Significant reduction in HOMA-IR score was found after 3 and 6 months with 1500mg/day metformin (4.34 ± 0.54) and (3.03 ± 0.48)(P<0.01) respectively compared to pre-treatment level.

Similarly, HOMA-Bscore was significantly low among patient group (20.32 ± 1.90) compared to the control subjects (192.31 ± 72.19)(P<0.05) at the pre-treatment level. Significant increase in HOMA-B score was noticed after 3 and 6 months with 1500mg/day metformin (29.43 ± 4.81)and (44.60 ± 10.18)(P<0.01) respectively compared to pre-treatment level.

Total but not free testosterone was significantly high in patient group (4.36 ± 0.72 ng/ml) compared to control subjects (3.18 ± 0.72 ng/ml) (P<0.05) at the pre-treatment level.

Significant decrease was noticed in total testosterone after 3 and in free testosterone after 6 months of treatment compared to pre-treatment level (3.83 ± 0.64 vs 3.33 ± 0.58 ng/ml) and (0.82 ± 0.11 vs 0.74 ± 0.02 ng/ml) (P<0.01) respectively.

Serum prolactin level was significantly higher among patient group (32.17 ± 8.19 ng/L) compared to controls (10.83 ± 3.19ng/L) (P<0.05) at the pre-treatment level. Significant reduction in prolactin level was found after 3

and 6 months with 1500mg/day metformin (28.93 ± 7.77 ng/L) and (23.23 ± 0.69ng /L) (*P*<0.01) respectively.

Correlation between glycemic parameters and endogenous hormones

The results showed no significant correlation between FBG with total testosterone, free testosterone, and serum prolactin levels at pre-treatment and after metformin therapy. There was significant negative correlation between FSI level and free testosterone at pre-treatment and after 3 months (*P*<0.05), and positive correlation with serum prolactin level only after 6 months of metformin therapy (*P*<0.05). HOMA-IR was negatively correlated with free testosterone at pre-treatment and after 6 months of metformin therapy (*P*<0.05). HOMA-B did not show any correlation with any endogenous hormone (table 2).

Correlation between HOMA-IR and HOMA-B with glycemic parameters

Correlation between HOMA-IR and HOMA-B with fasting serum insulin level and fasting blood glucose level in this study were illustrated in table (3). HOMA-IR was significantly positive correlated with FBG and FSI, and significant negatively correlated with HOMA-Bat pre-treatment and after 3 and 6 months of treatment (*P*<0.01). While HOMA-B showed significant negative correlation with FBG at pre-treatment and during treatment period, but significantly correlated with FSI at pre-treatment only (*P*<0.01).

Correlation between prolactin and endogenous hormones

The results showed no significant correlation between serum prolactinlevel with total testosterone and free testosteronebefore and after metformin therapy (table 4).

Table 1: Changes in glycemic parameters, β cell function, insulin resistance, and endogenous hormones at baseline level and after metformin therapy compared to healthy controls

Parameters	period	T2DM Treated with 1500mg/day (n=20)	Control (n=18)
Fasting Serum Glucose(mmol/L)	Pre-treatment	13.03 ± 0.74*	4.57 ± 0.33
	After 3 months	10.18 ± 1.15*†[a]	-
	After 6 months	7.6944 ± 1.06*†[b]	-
Fasting Serum Insulin (mU/ml)	Pre-treatment	9.63 ± 0.44	9.28 ± 0.88
	After 3 months	9.58 ± 0.40[a]	-
	After 6 months	8.85 ± 0.42†[b]	-
HOMA-IR	Pre-treatment	5.56 ± 0.40*	1.88 ± 0.22
	After 3 months	4.34 ± 0.54*†[a]	
	After 6 months	3.03 ± 0.48*†[b]	
HOMA-B	Pre-treatment	20.32 ± 1.90*	192.31 ± 72.19
	After 3 months	29.43 ± 4.81*†[a]	-
	After 6 months	44.60 ± 10.18*†[b]	-
Free testosterone (ng/ml)	Pre-treatment	0.82 ± 0.11	0.86 ± 0.12
	After 3 months	0.79 ± 0.08†[a]	-
	After 6 months	0.74 ± 0.02*†[b]	-
Total testosterone (ng/ml)	Pre-treatment	4.36 ± 0.72*	3.18 ± 0.72
	After 3 months	3.83 ± 0.64*†[a]	-
	After 6 months	3.33 ± 0.58†[b]	-
Serum prolactin (ng/L)	Pre-treatment	32.17 ± 8.19*	10.83 ± 3.19
	After 3 months	28.93 ± 7.77*†[a]	-
	After 6 months	23.23 ± 0.69*†[b]	-

Data were expressed as mean±SD; n=number of patients; *P<0.05 with respect to control group; †P<0.05 with respect to pre-treatment value; a,b P<0.01 between 3 and 6 months.

Table 2: Correlation between glycemic parameters and endogenous hormones at baseline and after metformin therapy

Variables/ days	Free Testosterone	Total Testosterone	Prolactin
Fasting Serum Glucose			
Pre-treatment	-0.409(p=0.092)	0.169(p=0.502)	0.201(p=0.424)
After 3 months	-0.281 (p=0.258)	0.102 (p=0.688)	0.244 (p=0.328)
After 6 months	-0.390 (p=0.110)	0.284 (p=0.254)	0.133(p=0.598)
Fasting Serum Insulin			
Pre-treatment	-0.501*(p=0.034)	-0.044(P=0.862)	0.273(p=0.273)
After 3 months	-0.530*(p=0.024)	-0.020 (P=0.939)	0.444(p=0.065)
After 6 months	-0.452 (p=0.060)	0.089(p=0.725)	0.652**(p=0.003)
HOMA-IR			
Pre-treatment	-0.664**(p=0.003)	0.132(p=0.602)	0.332(p=0.178)
After 3 months	-0.401 (p=0.099)	0.093 (p=0.713)	0.299 (p=0.229)
After 6 months	-0.483*(P=0.043)	0.308(p=0.214)	0.288(p=0.246)
HOMA-B			
Pre-treatment	0.079(p=0.757)	-0.177(p=0.483)	-0.019(p=0.940)
After 3 months	0.130 (p=0.608)	-0.147 (p=0.560)	-0.176(p=0.485)
After 6 months	0.313(p=0.206)	-0.252(p=0.313)	-0.039(p=0.877)

**. Correlation is significant at the 0.01 level (2-tailed); *. Correlation is significant at the 0.05 level (2-tailed).

Table 3: Correlation between HOMA-IRand HOMA-B with glycemic parameters at baseline and after metformin therapy

Variables/ days	FBG	FSI	HOMA-B
HOMA-IR			
Pre-treatment	0.773**(p=0.000)	0.590*(p=0.010)	-0.314 (p=0.204)
After 3 months	0.936** (p<0.01)	0.500* (p=0.034)	-0.805** (p<0.01)
After 6 months	0.959** (p<0.01)	0.533* (p=.023)	-0.896** (p<0.01)
HOMA-B			
Pre-treatment	-0.844**(p=0.000)	0.580* (p=0.012)	
After 3 months	-0.957** (p<0.01)	0.068 (p=0.788)	–
After 6 months	-0.977** (p<0.01)	-0.144 (p=0.568)	

**. Correlation is significant at the 0.01 level (2-tailed); *. Correlation is significant at the 0.05 level (2-tailed).

Table 4: Correlation between prolactin and endogenous hormones at baseline and after metformin therapy

Variables/ days	Free Testosterone	Total Testosterone
Prolactin		
Pre-treatment	-0.339(p=0.169)	-0.185(p=0.462)
After 3 months	-0.206(p=0.413)	-0.168 (p=0.505)
After 6 months	-0.269(p=0.280)	-0.202(p=0.422)

**. Correlation is significant at the 0.01 level (2-tailed); *. Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

Therapies targeting the maintenance of the protecting pancreatic beta-cells from injury or death might be crucial in the treatment of diabetes. It is well known that metformin enhances the expression of Glucagon-Like Peptide -1R via a peroxisome proliferator-activated receptor- (PPAR-) α-dependent mechanism, and improves the responsiveness to incretins.[22] The present study revealed several changes at the baseline level and following the administration of metformin in middle-aged premenopausal type 2 diabetic women in respect to the glycemic parameters, insulin resistance, β cell function, and endogenous hormones.

Needless to say that at the baseline level of the present study, diabetes related metabolic abnormalities showed marked changes in premenopausal type 2 diabetic women compared to that in non-diabetic controls , in addition to the increase in insulin resistance and the noticed reduction in β cell function expressed by the HOMA-B score (P<0.05).

The premenopausal type 2 diabetic women, in the present study, have an increase in endogenous testosterone at the baseline level (P<0.05), although inverse level in other studies.[18] There was also significant increase in serum prolactin at the baseline compared to non-diabetic controls (P<0.05). The support of this result is hypothesis via cellular studies which show the lactogenic hormone increase prolactin receptor expression on β-cells, induce β-cell replication and increase glucose-stimulated insulin secretion (GSIS), since the prolactin receptor is highly expressed at the pancreatic b-cell.[23, 24] Other large scale population-based study reporting a cross-sectional inverse association between prolactin and prevalent type 2 diabetes in both genders.[25]

Following three to six months with metformin therapy, significant improvement in glycemic parameters, insulin resistance, β cell function was clear(P<0.05). Similarly for endogenous testosterone and serum prolactin levels (P<0.05).

At the baseline, fasting serum insulin showed significant correlation with both HOMA- IR and HOMA-B, and after 6 months of treatment it was inversely correlated with HOMA-B only(P>0.05), speculating that reducing FSI via metformin cause improving of β cell function expressed by HOMA-B.

Fasting serum insulin positively correlated only with serum prolactin after 6 months of metformin therapy (P<0.05).Thus the reduction in serum prolactin following metformin therapy may potentially improves fasting serum insulin and IR.[21]

Since chronic hyperprolactinemia patients have postprandial hyperinsulinemia and an exaggerated insulin secretary response to glucose.[26] The direct dual effect of metformin on both pathophysiological conditions will be expected to improve β-cell function more.

No direct correlation was noticed between endogenous testosterone and serum prolactin (P>0.05), possibly due to the complex cross-talk between endogenous hormone receptors and insulin receptor.

Fasting serum insulin and IR showed significant negative correlation with free testosterone at the baseline and after metformin therapy (P<0.05). Hyperinsulinemic premenopausal type 2 diabetic women may have increase (or decrease) in endogenous testosterone level according to previous studies.[17, 18] The reduction in endogenous testosterone level after metformin therapy (P<0.05) correlated with improvement of insulin resistance.

Among most of the interventions preventing the deterioration of β-cell function, metformin improves β-cell function more effectively than other oral hypoglycemic drugs in type 2 diabetes patients.[27, 28]

CONCLUSION

In the present study, the reduction in serum prolactin and endogenous total and free testosterone following metformin therapy may potentially reduce fasting serum insulin, insulin resistance, and thereby improves β cell function in premenopausal type 2 diabetic women. Larger scale and longer duration of treatment may better explore these potential relationships.

REFERENCES

1. Marlon E. Cerf, Beta cell dysfunction and insulin resistance, *Frontiers in Endocrinology Diabetes*, Volume 4 (37), 2013, 1-12

2. McCarthy M.I.Genomics, type 2 diabetes, and obesity, *N. Engl.J. Med.*363, 2010, 2339–2350.

3. Voight B.F., Scott L.J., Steinthors- dottir V., Morris A.P., Dina C., Welch R.P., *etal*, Twelve type2diabetessusceptibilityloci identifiedthrough large scaleassociationanalysis, *Nat.Genet.*, 42, 2010, 579–589.

4. Ashcroft F.M., and Rorsman P, Diabetes mellitus and the beta cell: the last ten years, *Cell*, 148, 2012, 1160–1171.

5. Wallace TM, Levy JC, Matthews DR, Use and abuse of HOMA modeling. Diabetes care, Jun1; 27(6), 2004, 1487-95.

6. Prentki, M., and Nolan, C.J., Islet b cell failure in type 2 diabetes, *J. Clin. Invest, 116,* 2006, 1802–1812

7. Abel, E.D., et al., Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver, *Nature, 409,* 2001*,* 729–733.

8. Brandebourg T, Hugo E, Ben-Jonathan N, Adipocyte prolactin: regulation of release and putative functions. Diabetes ObesMetab, 9(4), 2007, 464-476.

9. Ben-Jonathan N, Hugo ER, Brandebourg TD, LaPensee CR: Focus on prolactin as a metabolic hormone. Trends in endocrinology and metabolism.TEM, 17(3), 2006, 110-116.

10. Brelje TC, Stout LE, Bhagroo NV, Sorenson RL: Distinctive roles for prolactin and growth hormone in the activation of signal transducer and activator of transcription 5 in pancreatic islets of Langerhans, Endocrinology ,145(9), 2004, 4162-4175.

11. Freemark M, Avril I, Fleenor D, Driscoll P, Petro A, Opara E, Kendall W, Oden J, and Bridges S, Binart N: Targeted deletion of the PRL receptor: effects on islet development, insulin production, and glucose tolerance, Endocrinology, 143(4), 2002, 1378-1385.

12. Serri O, Li L, Mamputu JC, Beauchamp MC, Maingrette F, Renier G: The influences of hyperprolactinemia and obesity on cardiovascular risk markers: effects of cabergoline therapy. ClinEndocrinol (Oxf), 64(4), 2006, 366-370.

13. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, et al. Diabetes in Asia: Epidemiology, Risk Factors, and Pathophysiology. JAMA, 301, 2009, 2129-40.

14. Mingrone G, Manco M, Iaconelli A, Gniuli D, Bracaglia R, Leccesi L, Calvani M, Nolfe G, Basu S, Berria R: Prolactin and insulin ultradian secretion and adipose tissue lipoprotein lipase expression in severely obese women after bariatric surgery. Obesity (Silver Spring), 16(8), 2008, 1831-1837.

15. J.M.Brand , C. Frohn, K.Cziupka, C.Brockmann, H.Kirchner and J.Luhm , Prolactin trigger proinflammatory immune response in peripheral immune cells .Eur cytokine Netw , 15(2), 2004, 99-104.

16. H.Orbach and Y.Shoenfeld .Hyperprolactinemia and autoimmune diseases, Autoimmune Rev, 6(8), 2007, 537-542.

17. Kim SY, Sung YA, Ko KS*et al ,* Direct relationship between elevated free testosterone and insulin resistance in hyperprolactinemic women. The Korean J journal of Internal Medicine, 8(1), 1993, 8-14.

18. Khalaf BH, Abdulridha MK ,Tuma WE, Najim HD, Effect of Endogenous Insulin Levels on Serum Testosterone, Glycemic, and ObesityParameters in Premenopausal Women with Type 2 Diabetes Mellitus, *UK Journal of Pharmaceutical and Biosciences*, 3(2), 2015, 60-67.

19. Yingling Jiang, Wei Huang, Jing Wang, Zhipeng Xu, Jieyu He, Xiaohong Lin, Zhiguang Zhou, Jingjing Zhang, Metformin Plays a Dual Role in MIN6 Pancreatic β Cell Function through AMPK-dependent Autophagy, *Int. J. Biol. Sci., 10(3),* 2014, 268-277.

20. Lu J, Zang J, Li H., Impact of Three Oral Antidiabetic Drugs on Markers of b-Cell Function in Patients with Type 2 Diabetes: A Meta-Analysis. *PLoS ONE*, 8(10), 2013, e76713. doi:10.1371/journal.pone.0076713

21. Khalaf BH. The effect of long term administration of metformin on prolactin level and C-reactive protein in newly diagnosed women with type II diabetes mellitus, *World Journal of Pharmacy and Pharmaceutical Sciences*, 4(06), 2015, 156-169.

22. Alessandra Puddu, Roberta Sanguineti, François Mach, Franco Dallegri, Giorgio Luciano Viviani, and Fabrizio Montecucco, Update on the protective molecular pathways improving pancreatic beta-cell dysfunction, *Mediators of Inflammation*, vol. 2013, 2013, p. 750540-54

23. Huang C, Snider F, Cross JC. Prolactin receptor is required for normal glucose homeostasis and modulation of beta-cell mass during pregnancy, *Endocrinology, 150,* 2009, 1618e26.

24. Labriola L, Montor WR, Krogh K, Lojudice FH, Genzini T, Goldberg AC, Beneficial effects of prolactin and laminin on human pancreatic islet-cellcultures, *Mol Cell Endocrinol*, 263, 2007, 120e33.

25. Lisa Balbach, Henri Wallaschofski1, Henry Völzke, Matthias Nauck, Marcus Dörr, and Robin Haring, Serum prolactin concentrations as risk factor of metabolic syndrome or type 2 diabetes? *BMC Endocrine Disorders* , 13, 2013, 12-20

26. Caroline M. Gorvin. The prolactin receptor: Diverse and emerging roles in pathophysiology, *Journal of Clinical & Translational Endocrinology*, 2, 2015, 85-91.

27. Lu J, Zang J, Li H. Impact of three oral antidiabetic drugs on markers of beta-cell function in patients with type 2 diabetes: a meta-analysis. PLOS ONE, 8(10), 2013, e76713.

28. Bi Y, Tong GY, Yang HJ, Cai MY, Ma JH, Liang J, Xin B, Miao H, Peng ZH, Zhu DL. The beneficial effect of metformin on β-cell function in non-obese Chinese subjects with newly diagnosed type 2 diabetes.*Diabetes Metab Res Rev.* , 29(8), 2013, 664-72.

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