Sir,

Polycystic ovary syndrome (PCOS) is the most frequently encountered endocrine-metabolic disorder among reproductive-aged females. PCOS is frequently associated with insulin resistance (IR), hyperinsulinemia, obesity, and cardio-metabolic co-morbidities.[1] The general consensus is that obese PCOS women are resistant to insulin and that PCOS appears to intensify the adverse effects of obesity on IR.[2] One of the most common strategies in targeting IR in PCOS is the use of insulin-sensitizers, in particular metformin. A prospective interventional study conducted at Al-Yarmouk Teaching Hospital between January 2019 and April 2020. The study was approved by the Local Ethical Committee. A total of 71 obese PCOS women were included. They were allocated into three sub-groups according to the WHO classification of obesity into: Class I (BMI of 30-34.99 kg/m$^2$), Class II (BMI of 35-39.99 kg/m$^2$), and Class III (BMI ≥40 kg/m$^2$). Diagnosis of PCOS was made according to modified Rotterdam criteria.[3]

The subjects were assigned to receive metformin 1500 mg daily in three divided doses for three months. Fasting plasma glucose, fasting serum insulin, total serum testosterone, and glycosylated hemoglobin (HbA1c) were measured before and after treatment. BMI, HOMA-IR, and insulin sensitivity (IS) were calculated. Data analysis was done using paired-t-test, ANOVA test, and least significant difference (LSD) test with $P$ value ≤ 0.05 considered significant.

Metformin provided a significant reduction in BMI, serum testosterone, fasting glucose, fasting insulin, and HOMA-IR with a significant improvement in IS and HbA1c in all obesity classes. The percent change in fasting glucose, fasting insulin, HOMA-IR, and IS significantly differ between different obesity classes [Table 1]. Using LSD test, changes were significant when comparing class III with I for fasting glucose ($P = 0.028$) and class II with I for fasting insulin, HOMA-IR, and IS with $P$ values of 0.011, 0.008, and 0.009, respectively.

This study shows that short-term treatment with metformin is sufficient in attenuating IR besides reducing weight which is in concordance with previous reports.[4] Women with PCOS are at greater risk for cardiovascular events, prediabetes, and type 2 diabetes mellitus as they share people with diabetes a similar pattern of impaired glucose metabolism; putting in mind these facts, metformin role in diabetes prevention, and the American Diabetes Association recommendation for using metformin in people with prediabetes in particular for those with BMI ≥35 kg/m$^2$, all these consolidate our findings. Till now there is no clear answer for how long we need to treat women with PCOS using metformin. When we consider the short duration of metformin treatment in this study and the long-term sequel of PCOS especially in obese women, extending the treatment duration is crucial for the aim of reducing these risks. The strength of this study is in support of using metformin selectively for obese PCOS women with BMI of ≥35 kg/m$^2$. Limitation includes small sample size. Further studies with larger sample sizes and for longer duration of therapy are needed, this represents another scope of a second research we are processing now.

The Effect of Short-term Treatment with Metformin on Insulin Resistance among Obese Iraqi Women with Polycystic Ovary Syndrome
Table 1: The comparison of the three different groups according to BMI, testosterone, fasting glucose, fasting insulin, HOMA-IR, insulin sensitivity and HbA1c before and after metformin use

|                      | Class I (n=44) | Class II (n=20) | Class III (n=7) | P       |
|----------------------|---------------|-----------------|-----------------|---------|
| **BMI (Kg/m²)**      |               |                 |                 |         |
| Before               | 31.3±1.25     | 36.9±1.54       | 45.4±3.59       | 0.0001* |
| After                | 29.7±1.14     | 34.9±1.43       | 42.6±3.76       | 0.0001* |
| %Difference          | -5.0±1.5      | -5.6±1.4        | -6.0±1.0        | 0.128   |
| P value              | 0.0001*       | 0.0001*         | 0.001*          |         |
| **Total testosterone (nmol/L)** |            |                 |                 |         |
| Before               | 1.4±0.33      | 1.91±0.33 (1.20-2.776) | 2.49±0.26 (1.978-2.70) | 0.0001* |
| After                | 1.28±0.33 (0.79-2.00) | 1.67±0.29 (0.90-2.30) | 2.13±0.21 (1.874-2.40) | 0.0001* |
| %Difference          | -11.5±3.1     | -12.8±3.8       | -14.5±5.3       | 0.090   |
| P value              | 0.0001*       | 0.0001*         | 0.001*          |         |
| **Fasting glucose (mmol/L)** |            |                 |                 |         |
| Before               | 5.40±0.33 (4.7-5.9) | 5.65±0.30 (5.0-6.2) | 5.74±0.15 (5.6-5.9) | 0.002*  |
| After                | 5.19±0.27 (4.6-5.7) | 5.39±0.25 (4.8-5.8) | 5.41±0.13 (5.3-5.6) | 0.006*  |
| %Difference          | -3.9±2.0      | -4.6±1.5        | -5.7±1.2        | 0.048*  |
| P value              | 0.0001*       | 0.0001*         | 0.001*          |         |
| **Fasting insulin (µU/mL)** |            |                 |                 |         |
| Before               | 14.6±4.65 (6.69-26.54) | 18.33±4.64 (10.80-25.90) | 23.32±4.53 (17.698-28.598) | 0.0001* |
| After                | 10.96±3.67 (6.10-20.10) | 12.93±3.65 (6.30-18.20) | 17.79±4.34 (11.80-23.50) | 0.0001* |
| %Difference          | -25.1±6.2     | -29.7±6.7       | -24.4±4.8       | 0.023*  |
| P value              | 0.0001*       | 0.0001*         | 0.001*          |         |
| **HOMA-IR**          |               |                 |                 |         |
| Before               | 3.54±1.19 (1.427-6.841) | 4.60±1.20 (2.634-6.563) | 5.97±1.27 (4.404-7.499) | 0.0001* |
| After                | 2.54±0.90 (1.274-5.002) | 3.10±0.91 (1.596-4.539) | 4.29±1.10 (2.779-5.640) | 0.0001* |
| %Difference          | -28.2±6.4     | -32.9±6.4       | -28.7±4.0       | 0.023*  |
| P value              | 0.0001*       | 0.0001*         | 0.001*          |         |
| **Insulin sensitivity** |            |                 |                 |         |
| Before               | 0.31±0.10 (0.146-0.701) | 0.23±0.07 (0.152-0.379) | 0.17±0.04 (0.133-0.227) | 0.0001* |
| After                | 0.43±0.13 (0.199-0.785) | 0.35±0.11 (0.220-0.626) | 0.25±0.07 (0.177-0.3598) | 0.0001* |
| %Difference          | 40.4±13.1     | 50.4±15.5       | 40.8±8.5        | 0.024*  |
| P value              | 0.0001*       | 0.0001*         | 0.0001*         |         |
| **HbA1c (%)**        |               |                 |                 |         |
| Before               | 5.37±0.32 (4.5-6.0) | 5.51±0.32 (5.1-6.3) | 5.83±0.41 (5.2-6.4) | 0.003*  |
| After                | 5.14±0.30 (4.4-5.8) | 5.26±0.29 (4.9-6.0) | 5.57±0.35 (5.0-6.0) | 0.003*  |
| %Difference          | -4.2±1.5      | -4.5±1.0        | -4.4±1.7        | 0.727   |
| P value              | 0.001*       | 0.001*          | 0.001*          |         |

-Data were presented as Mean±SD (Range). *Significant difference among more than two independent means using ANOVA-test at 0.05 level. †Significant difference between two dependent means using Paired-t-test at 0.05 level.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Sir,

In animal models, incretin‑based therapy has been shown to be effective in protecting and preserving β‑cell functions.[1] Farilla et al 2002 and Li et al 2003  have corroborated that DPP‑4 inhibitors increase islet cell proliferation, and decrease cell apoptosis[2].

However, as with any other drugs we need to be aware of the adverse effects of Sitagliptin so that it may be withdrawn at the very advent of any adverse reaction. The adverse skin manifestations of Sitagliptin are all the more important because reports have illustrated their appearance almost 6 months after initiation of therapy;[3] thus if the physician is unaware of these uncommon reactions then both the physician and the patient would be baffled and puzzled by these manifestations. Obviously, the drug will not be withdrawn because it will be the least suspected culprit and the patient would be left battling with these manifestations indefinitely.

A 60‑year‑old woman came to our outdoor department with the complaint of generalized skin lesion for the last 3 months. Distribution of lesions around umbilicus, lower back, lower extremities, and face is shown in Figures 1‑5. She was diagnosed as a case of Type 2 diabetes mellitus about 1 year back and she was taking one tablet of Sitagliptin 50 mg + Metformin 500 mg twice a day since then as advised by her physician with proper follow up. Her blood sugar levels were well under controlled with this regime, HbA1c 6.8%, fasting blood sugar 98 mg/dL, postprandial blood sugar 165 mg/dL. She developed these skin lesions at 3 months of following this said regime. She has never had any skin disease in past nor history of any fixed drug eruption in past. Her vitals were stable and her general and systemic examinations were within normal limits. Her complete blood count, liver function test, kidney function test, lipid profile were within normal limits. Anti‑HCV, HBsAg, HIV, and VDRL were non‑reactive. Her chest X‑ray, ultrasonography of abdomen, fundus examination were normal. On searching through web journals and case reports we found out that there exists association of such skin lesion with the use of Sitagliptin + Metformin regime. On consultation with our dermatology department, we made the diagnosis of drug‑induced Papulonodular lesions in a patient of Diabetes Mellitus receiving Sitagliptin and Metformin. As both Sitagliptin and Metformin can cause papulonodular lesion as mentioned in literature[4] so we cannot discriminate whether it is due to which drug.

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How to cite this article: Findakly SB, Sersam LW. The effect of short‑term treatment with metformin on insulin resistance among obese Iraqi women with polycystic ovary syndrome. Indian J Endocr Metab 2021;25:354‑6.

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