

# Continuous glucose monitoring in polycystic ovary syndrome: what interest?

ines kammoun (✉ [ines.kammoun@fmt.utm.tn](mailto:ines.kammoun@fmt.utm.tn))

Universite de Tunis El Manar <https://orcid.org/0000-0002-8322-5621>

**Wafa Ben Saada**

Department of endocrinology and metabolic diseases, Institut national de Nutrition, Tunis

**Hajer Kandara**

Department of endocrinology and metabolic diseases, institut National de Nutrition, Tunis

**Radhouane Gharbi**

Department of endocrinology and metabolic diseases, Institut National de Nutrition, Tunis

**Rania Ben Said**

Department of endocrinology and metabolic diseases, Institut National de Nutrition, tunis

**Claude Ben Slama**

Department of endocrinology and metabolic diseases, Institut National de Nutrition, Tunis

**Manel Jemel**

Department of endocrinology and metabolic diseases, Institut National de Nutrition, tunis

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## Research article

**Keywords:** polycystic ovary syndrome, carbohydrate metabolism, continuous glucose monitoring, subclinical abnormalities

**Posted Date:** February 3rd, 2020

**DOI:** <https://doi.org/10.21203/rs.2.22520/v1>

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# Abstract

## Purpose

The aim of our study was to detect subclinical abnormalities in carbohydrate metabolism in patients with polycystic ovary syndrome.

## Methods

Cross-sectional study including 20 patients with PCOS diagnosed according to 5- the Rotterdam criteria. All the patients had normal carbohydrate tolerance (fasting blood glucose <5.6 mmol/l, 2-h plasma glucose after a 75-g oral glucose tolerance test <7.8 mmol/l and glycated hemoglobin <5.8%). For each patient, we performed a continuous glucose monitoring over 72h, measuring the interstitial glucose every 5 minutes (288 measurements per day). We collected data about: the mean blood glucose, obtained by determining the mean values of the 288 measurements made by 24h - the mean amplitude of glycemic excursions, which is the difference between the maximum and minimum glycemic values - the time (in hours) in which the blood glucose was <0.7 g/l and / or >1.4 g/l.

## Results

The mean blood glucose (over 72h) was  $0.94 \pm 0.07$  g/l (0.81-1.11). The mean amplitude of glycemic excursions (over 72h) was  $0.81 \pm 0.23$  g/l (0.47-1.31). Fourteen patients (pathologic group) had subclinical glycemic abnormalities: 14 patients had glycemic values <0.7 g/l and 5 patients had also glycemic values >1.4 g/l. The mean amplitude of glycemic excursions was significantly lower ( $p=0.016$ ) in the normal group (6 patients, 0.64 g/l) compared to the pathologic group (14 patients, 0.88 g/l). The other clinical and biological parameters were comparable between the two groups.

## Conclusions

Our findings confirm the high frequency of subclinical abnormalities of carbohydrate metabolism in patients with polycystic ovary syndrome. A regular follow-up of these patients is necessary.

## Background

Polycystic ovary syndrome (PCOS) is one of the most common female endocrinopathies, with a prevalence of around 15% in women of childbearing age [1]. This dual reproductive and metabolic disease can be responsible for hyperandrogenism, fertility and menstrual cycle disorders, obesity, diabetes mellitus (DM), dyslipidemia, hypertension, and even endometrial cancer [2]. Insulin resistance (IR) appears to be the link between these different anomalies.

Very few studies have examined the glycemic profile of patients with PCOS and without clear alterations in glycoregulation. These studies [3, 4] have demonstrated the existence of subclinical glycoregulation abnormalities, which may subsequently lead to a state of glucose intolerance or even to DM.

The aim of our study was to detect subclinical abnormalities in glucose metabolism in patients with PCOS by using a 72-hour continuous glucose monitoring (CGM).

## Methods

We conducted a cross-sectional study that included 20 patients with PCOS, followed at the department of endocrinology and metabolic diseases of the National Institute of Nutrition (Tunis). We chose this number of participants with reference to the literature since the studies made on this subject did not exceed 10 to 45 patients.

The total duration of recruitment was 08 months (from April to November 2013).

### I - Patients:

#### Inclusion Criteria

- Age : 18-45 years old
- Diagnosis of PCOS confirmed according to the Rotterdam 2003 criteria [5], by the presence of at least 2 of the 3 following criteria:
  - Clinical (hirsutism) and/or biological (total testosterone > 2 nmol / l) hyperandrogenism
  - Dysovulation: occurrence of fewer than 9 menstruations per year
  - PCOS echographic criteria: ovarian volume> 10 ml and/or the presence of  $\geq 12$  follicles (2-9 mm) on one or both ovaries.
- Normal carbohydrate tolerance attested by:
  - Fasting blood glucose (FBG)<5.6 mmol / l and
  - 2-h plasma glucose <7.8 mmol / l (after a 75-g oral glucose tolerance test) and
  - Glycated hemoglobin (HbA1c) <5.8%.
- Informed Consent

#### Non-Inclusion Criteria

- Other etiologies of hyperandrogenism and/or menstrual disorders, including congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, hyperprolactinemia and hypothyroidism.
- Pregnant or breastfeeding women
- Patients who took, in the 3 months preceding the study, drugs interfering with the carbohydrate metabolism (corticotherapy, estrogens, metformin).

### II. Methodology:

#### 1. Data collected:

For each patient, we performed a clinical examination and metabolic assessment with fasting insulinemia (FI) and calculation of the HOMA-R index by the formula:

$$\text{HOMA-R} = (\text{FBG (mmol / l)} * \text{FI (}\mu\text{IU / ml)}) / 22.5$$

We also realized, for each patient, a CGM over 72 hours. The device used was the Medtronic Minimed CGMS. It consists of an implantable electrode in the abdominal subcutaneous tissue, connected to a computer system that stores all the values of the measured signal. The implanted system makes it possible to obtain an interstitial glucose value every 5 minutes (288 measurements per day).

In order to obtain an optimal recording, 4 capillary blood glucose per day (before the 3 meals and before bedtime) were measured to calibrate the system.

The implantation of the device was performed in all patients at the same time (between 9am and 11am). We asked them to maintain their eating habits and their usual professional and physical activities.

From the CGM, we noted:

- The mean blood glucose (MBG, expressed in g/l) obtained by determining the average values of the 288 measurements made by 24h.
- The mean amplitude of the glycemic excursions (MAGE, expressed in g / l) represented by the difference between the maximum and minimum values of the blood glucose levels
- The length of time (in hours) when blood glucose was <0.7 g / l and / or> 1.4 g / l.

We then divided our patients into 2 groups:

- Patients in whom blood glucose levels were still between 0.7 and 1.4 g / l during 72 hours: normal CGM group
- Patients in whom blood glucose levels were outside these limits: pathological CGM group

We compared the clinical and biological parameters of these two groups.

Informed consent was obtained from all participants included in the study.

2- Data analysis:

We calculated:

- simple and relative frequencies (percentages) for qualitative variables.
- means and standard deviations with determination of extreme values for the quantitative variables.

The comparison of means on independent series was performed using the non-parametric Mann and Whitney test.

The comparison of percentages on independent series was performed by the Pearson chi-square test, and in case of non-validity of this test, by Fisher's exact bilateral test.

The study of the link between 2 quantitative variables was made by Spearman's correlation coefficient.

For all statistical tests, the threshold of statistical significance was set at  $p < 0.05$ .

## Results

The mean age of our patients was  $26.2 \pm 6.6$  years (18 to 45 years). The mean body mass index BMI was  $32.9 \pm 8.7$  Kg / m<sup>2</sup> (20-55). Twenty percent of our patients were overweight and 65% were obese.

The mean value of MBG (over 72 hours) was  $0.94 \pm 0.07$  g / l (0.81 - 1.11).

The mean value of the MAGE (over 72 hours) was  $0.81 \pm 0.23$  g / l (0.47 - 1.31).

The blood glucose levels remained between 0.70 and 1.40 g / l during the 72 hours of the recording in 6 cases among our 20 patients.

Fourteen patients had blood glucose  $< 0.70$  g / l during the recording, five of whom had blood glucose  $< 0.50$  g / l and five other patients had also a blood glucose level  $> 1.40$  g / l (Figure 1). Hypoglycemia was asymptomatic and not felt by patients.

The length of time spent outside the previously fixed limits ( $< 0.7$  or  $> 1.4$  g / l), expressed in hours, is detailed in table 1.

The MBG and MAGE values were not significantly correlated with the different clinical and biological parameters studied (BMI, waist circumference, FBG, HbA1c, FI and HOMA index).

We divided our patients into 2 groups based on CGM data:

- Normal CGM group: patients in whom blood glucose levels were always between 0.7 and 1.4 g / l during the 72 hours (n = 6)
- Pathological CGM group: patients who had blood glucose levels outside these limits (n = 14)

We found no significant difference between these 2 groups concerning BMI, waist circumference, presence of acanthosis nigricans, menstrual disorders, family history of diabetes, FBG, HbA1c, FI, HOMA index, and total testosterone (table 2).

The value of the MBG was also comparable in both groups ( $0.97 \pm 0.05$  vs  $0.93 \pm 0.07$  g/l). However, the MAGE value was significantly lower in the group with normal registration ( $0.64$  vs  $0.88$  g / l,  $p = 0.016$ ).

## Discussion

In our 20 patients with PCOS who have had CGM, the blood glucose values remained in the range of 0.70-1.40 g / l in only 6 patients during the 72 hours of recording. All the other 14 patients had blood glucose levels less than 0.70 g / l. This would be related most probably, to hyperinsulinism secondary to insulin resistance in these patients. Nevertheless, we found no significant difference between these 2 groups concerning clinical, metabolic or hormonal parameters.

This is the first Tunisian study to assess the results of CGM in patients with PCOS. However, our study has some limitations. It is mainly the absence of a control group which could not be included for financial reasons.

The association between hyper-androgenism and metabolic disorders was first described by Achard and Thiers in 1921 [6]. Subsequently, several epidemiological studies confirmed the high prevalence of carbohydrate tolerance abnormalities in women with PCOS [7, 8]. Indeed, the risk of DM is multiplied by 7 in these patients [9].

According to the American Diabetes Association (ADA), diabetes screening is recommended in PCOS patients, as the risk of progression to DM is 2-3% per year. This screening is made by a 75-g oral glucose tolerance test or HbA1c determination according to the ADA in 2018 [10].

CGM can record interstitial glucose values ranging from 0.4 to 4 g / l. It is more sensitive in the detection of strong glycemic variations [11]. It was initially used in diabetic subjects. Currently, it is also used in healthy subjects, pregnant women [12, 13] and even in the cardiac intensive care unit [14], to evaluate the effect of BMI, some foods, physical activity, and stress on blood glucose levels variations [13]. CGM is also used to diagnose early glycemic abnormalities in all high risk patients [15].

A Chinese study that performed CGM in 434 healthy volunteers [16] chose the range of normal blood glucose between 0.70 and 1.40 g / l. Another Italian study that included 15 healthy volunteers [13] set the normal range of blood glucose between 0.70 and 1.25 g / l. In our study, we chose the interval between 0.70 and 1.40 g/l, since the population of the Chinese study [16] was important and especially because in this study, the time spent outside the normal range was less than 1 hour over the entire 72 hours. This interval would therefore reflect the physiological variations of blood glucose.

Another Chinese study [3] performed continuous blood glucose recording in 20 patients with PCOS (with normal carbohydrate tolerance) and 20 age-matched healthy women with normal menstruation. MBG and MAGE were comparable in both groups. In contrast, the peaking time of post-breakfast plasma glucose level of the PCOS group was significantly longer than that of the control group. CGM diagnosed an abnormal mode of daily glucose change characterized by a delayed peak of post-breakfast plasma glucose level.

A third study [4] also performed CGM in 45 patients with PCOS with normal glucose tolerance and 45 age-matched controls female. Postprandial blood glucose was significantly higher in patients with PCOS.

Our study highlights some glycemic disorders that could predict a pre-diabetes condition in patients with PCOS. These disorders are undetectable on oral glycemic tolerance test and unpredictable by other clinical and biological parameters. Larger-scale controlled studies are needed to better clarify these data.

## Conclusion

PCOS is a common endocrine pathology in women of childbearing age. The metabolic disorders are frequent in these patients. The aim of our work was to look for subclinical abnormalities in carbohydrate metabolism using a 72 hours CGM, in 20 normoglycemic patients with PCOS.

The CGM has indeed highlighted some disorders, especially a low blood glucose and even authentic asymptomatic hypoglycaemia (<0.50 g /l). This profile could predict a pre-diabetes condition.

We emphasize the importance of early diagnosis and regular screening of metabolic anomalies in patients with PCOS. The CGM might be interesting for early detection of subclinical glycemic disorders.

## List Of Abbreviations

ADA: American Diabetes Association

BMI: body mass index

CGM: continuous glucose monitoring

DM: diabetes mellitus

FBG: Fasting blood glucose

FI: fasting insulinemia

HbA1c: glycated hemoglobin

IR: Insulin resistance

MAGE: mean amplitude of the glycemic excursions

MBG: mean blood glucose

PCOS: Polycystic ovary syndrome

## Declarations

**Ethical approval and consent to participate :** The study was approved by the ethics committee of the National Nutrition Institute of Tunis. Written informed consent was obtained from all participants.

**Consent for publication :** Not Applicable

**Availability of data and materials :** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

**Competing Interests:** The authors declare that they have no competing interests

**Funding:** This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

**Authors contributions:** IK participated in the conception, design of the work, interpretation of data and revision of the final manuscript. WBS have drafted the work. HK participated in the conception and analysis. RG participated in the writing of the manuscript. RBS participated in the acquisition of data. CBS substantively revised the manuscript. MJ participated in the acquisition of data. All authors read and approved the final manuscript.

**Acknowledgements:** Not Applicable

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## Tables

Table 1. Time spent outside the limits of 0.7-1.4 g/l

	1 <sup>st</sup> day	2 <sup>nd</sup> day	3 <sup>d</sup> day	Total of 72 hours
<b>G &gt; 1,40 g/l (n=5)</b>	0,04±0,17 H	0,08±0,3 H	0,3±0,6 H	0,14 H
<b>G &lt; 0,70 g/l (n=14)</b>	2,7±3 H	0,93±1,52 H	0,08±0,24 H	1,23 H

Table 2: Comparison between normal and pathological CGM group

	Normal CGM Group (n=6)	Pathological CGM Group (n=14)	p
Age (year)	26 ± 8,2	21,3 ± 7,4	ns
BMI (Kg/m <sup>2</sup> )	32,1 ± 10	33,2 ± 8	ns
Waistcircumference (cm)	97,5 ± 16,3	97,7 ± 15,4	ns
Acanthosisnigricans (n)	2	7	ns
Menstruel disorders (n)	4	12	ns
Family history of diabetes (n)	2	2	ns
FBG (mmol/l)	5,1 ± 0,26	5 ± 0,47	ns
HbA1c (%)	5,4 ± 0,2	5,3 ± 0,4	ns
FI (μUI/ml)	11,2 ± 8,5	24,14 ± 20	0,08
HOMA Index	2,5 ± 1,9	5,4 ± 4,6	ns
Testosterone (nmol/l)	2 ± 0,7	2,4 ± 0,6	ns

n: number      ns : not significant

## Figures

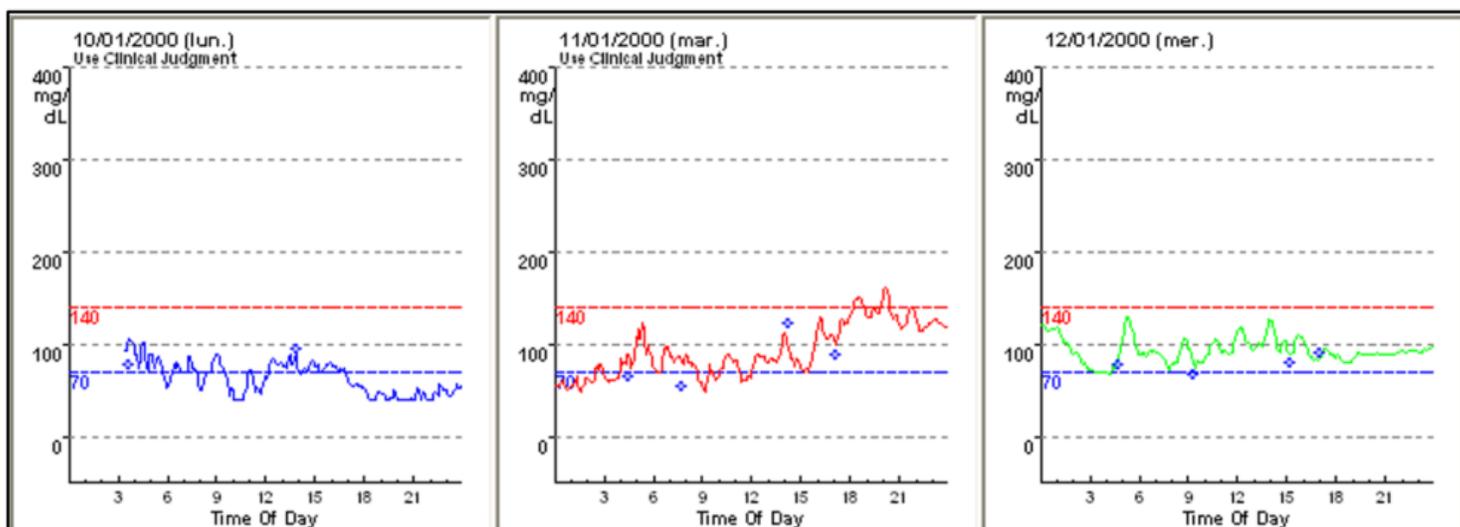


Figure 1

Continuous glucose monitoring showing subclinical glycemic abnormalities in our patients

## Supplementary Files

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- [STROBEchecklistcrosssectional.doc](#)