

Professional article

Can Continuous Glucose Monitoring Be Used as a New Tool for Diagnosing White Coat Hyperglycaemia and Possibly Some Other Entities?

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SUMMARY

Introduction. Since 1999 continuous glucose monitoring (CGM) has been used to measure the amount of glucose in the interstitial fluid. CGM is crucial when it comes to developing the ambulatory glucose profile and giving information on time spent in range (TIR), percentage of time spent above and below range, as well as variability.

Discussion. It was in 1992 that Campbell et al. first described white coat hyperglycaemia, who explained it as patients having elevated blood glucose levels in a clinician's office or laboratory and normal glucose levels obtained by self-monitoring. Prior to the introduction of CGM, white coat hyperglycaemia was described as the discrepancy in the levels of office glucose and self-monitoring blood glucose (SMBG). Nowadays, it may be said that a patient has white coat hyperglycaemia when they have elevated office levels and normal SMBG levels or TIR above 70% on CGM. Recognising white coat hyperglycaemia is of crucial importance for treatment as its intensification based on office glycaemia alone can lead to episodes of hypoglycaemia and a potentially lethal outcome. Should comparison be made with arterial hypertension and ambulatory blood pressure monitoring (ABPM), CGM may provide several other options: 1) masked hyperglycaemia; 2) isolated nocturnal hyperglycaemia.

Conclusion. It seems logical that CGM can be used for diagnosing white coat hyperglycaemia and possibly some (new) entities. Nonetheless, the clinical significance of all these entities can only be discussed after conducting adequately designed randomised clinical trials, which we would strongly encourage.

Keywords: diabetes mellitus, continuous glucose monitoring, white coat hyperglycaemia, ambulatory blood pressure monitoring

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INTRODUCTION

The analogy of ambulatory blood pressure monitoring and continuous glucose monitoring

The everyday use of ambulatory blood pressure monitoring (ABPM) has resulted in the introduction of two new entities of arterial hypertension – white coat hypertension (WCH) and masked arterial hypertension (MAHT). WCH is defined as having high office blood pressure (BP) values, while out-of-office monitoring, which includes ABPM and home blood pressure monitoring (HBPM), records normal values. On the other hand, patients with MAHT experience elevated out-of-office BP and normal office BP. This usually refers to treatment-naïve patients. In addition, two more entities have emerged recently – white coat uncontrolled hypertension (WCUH) and masked uncontrolled hypertension (MUCH). WCUH occurs in antihypertensive-treatment-receiving patients with high office BP and normal out-of-office BP. In contrast, MUCH patients receive antihypertensives and experience normal office BP but elevated out-of-office BP (1).

Since 1999, when it was approved by Food and Drug Administration, continuous glucose monitoring (CGM) has been used to measure the amount of glucose in the interstitial fluid. The device monitors blood sugar for 24 hours a day, performing continual checks every five minutes and continuously transmitting glucose readings, which can be observed by both patients and caregivers via a smartphone or reader. The extensive data given by CGM allows for more detailed analysis of patient data than was achievable in the past, thus offering extra information to help in meeting glycaemic goals. Therefore, it could be argued that using CGM devices should be enabled from the moment a person is diagnosed with diabetes mellitus (especially type 1) and in need of multiple daily injections or continuous subcutaneous insulin infusion (2).

It has been proved that the use of CGM:

- 1) reduces the values of glycosylated haemoglobin (A1c) (3);
- 2) reduces episodes of hypoglycaemia (4);
- 3) improves the quality of life by removing the need for frequent self-monitoring of blood glucose (SMBG) (5).

Adoption of CGM devices was enhanced by standardization of CGM metrics that was defined by

the panel of experts (6). The panel selected 10 metrics that can be the most useful in clinical practice. Three crucial measurements include time in range- time of the day within target glucose range (TIR- glucose measurements within 3.9 and 10.0 mmol/l), time below range (TBR- below 3.9 mmol/l), time above range (TAR- above 10.0 mmol/l).

The primary goal for effective and safe glucose control is to increase the TIR while reducing the TBR (6). Individual goals were set for different patient groups, but TIR above 70% is the most important goal, and this value correlates with HbA1c 7% in type 1 diabetes patients (7). There is also an association between TIR and diabetic complications – progression of diabetic retinopathy or development of microalbuminuria (8).

Furthermore, CGM can help reveal impaired adherence to treatment regimens in patients with DM. Usually, medication compliance is the highest immediately before and after the visit to the physician. White coat adherence (WCH) is defined as increased adherence to medical and other therapy regimens a couple of days prior to a visit to a healthcare provider (9). WCH is especially pronounced in DM patients with poor to moderated glycemic control (9). The clinical significance of WCH is that it can lead to wrong or missing therapy adaptations (10).

CGM is crucial when it comes to developing the ambulatory glucose profile and giving information on time spent in range, percentage of time spent above and below range, as well as variability. Glucose readings from CGM devices, which are standardised, single-page long, and have visual cues, should become standard reports for all CGM devices. The values on CGM that are considered normal include (11):

- time in range (TIR) above 70%;
- time above 10.0 mmol/l less than 25%;
- time below 3.9 mmol/l less than 4%.

CONTENT

White coat hyperglycaemia

It was in 1992 that Campbell et al. first described white coat hyperglycaemia, who explained it as patients having elevated blood glucose levels in a clinician's office or laboratory and normal glucose levels obtained by self-monitoring at home (12). It seems that, owing to the same pathogenesis, there is a significant correlation between white coat hyper-

glycaemia and white coat hypertension (13). This is so because the level of blood glucose, much like BP (14), can be risen by everyday stress as well as anxiety about being in a medical facility. Acute stress causes a rise in norepinephrine and cortisol, which can induce an increase in the level of glucose five minutes after the onset of acute stress and a delayed resolution within 90 minutes (15). Probably the main cause of white coat hyperglycaemia is gluconeogenesis: stress leads to lactate release, higher lactate concentration induces gluconeogenesis which then causes white coat hyperglycaemia (16). On the other hand, white coat hypertension is usually caused by higher levels of norepinephrine. This so called "white dual effect" should be suspected if the patient has white coat hypertension and high fasting blood glucose in laboratory settings and normal level of HbA1c (16).

White coat hyperglycaemia should be suspected when there is a large discrepancy between the levels of office glycaemia and those of A1c. However, having high levels of office glycaemia and normal levels of A1c does not always lead to white coat hyperglycaemia since daily glycaemic fluctuation does not often correlate with A1c. Moreover, A1c does not provide a measure of glycaemic variability or hypoglycaemia. This is of great importance since high glucose variability is associated with a higher complication rate (17). This is why glycaemic control is best estimated by the combination of results from CGM, SMBG and A1c.

Prior to the introduction of CGM, white coat hyperglycaemia was described as the discrepancy in the levels of office glucose and SMBG. Nowadays, it may be said that a patient has white coat hyperglycaemia when they have elevated office levels and normal SMBG levels or TIR above 70% on CGM.

Recognising white coat hyperglycaemia is of crucial importance for treatment as its intensification based on office glycaemia alone can lead to episodes of hypoglycaemia and a potentially lethal outcome (18). For example, if the results of measuring patient's glycaemic levels show ≥ 10 mmol/l for two consecutive mornings, the insulin dose will definitely be increased even with normal levels of SMBG and/or A1c. However, the patient's glycaemic levels may in fact be normal, but just being in a medical facility might cause stress hormones to be secreted and glycaemic levels to surge. Increasing the insulin dose in this case increases the possibility of hypo-

glycaemia.

Other possibilities

Should comparison be made with arterial hypertension and ABPM, CGM will provide several other options:

1) Masked hyperglycaemia, which would represent the counterpart of MAHT. This means that it would be defined by normal office glycaemic levels and elevated glycaemic levels during CGM or SMBG. A1c is of tremendous importance here. Namely, normal office glycaemic levels and elevated A1c levels suggest abnormal glucoregulation. Nevertheless, CGM can help with a titration of therapy. For example, normal glycaemic levels in the morning and substantially elevated levels in the evening indicate that the evening dose of rapid-acting insulin or the morning dose of basal insulin should be increased (depending on which insulin treatment is used and when the pathological values of glycaemia have been noted).

2) Isolated nocturnal hyperglycaemia. Just as there is isolated nocturnal hypertension (19), there may be isolated nocturnal hyperglycaemia. This entails normal glycaemic levels from 6 a.m. to 10 p.m. and their increase afterwards. For example, in patients with sleep apnoea, hypoxaemia results in the release of stress hormones that elevate BP as well as glycaemia during the night (20). When it comes to treatment, nocturnal glycaemic readings can aid in the differential diagnosis of two common conditions: the Somogyi effect and the dawn phenomenon (21).

CONCLUSION

It seems logical that CGM can be used for diagnosing white coat hyperglycaemia and possibly some (new) entities. Nonetheless, the clinical significance of all these entities (white coat hyperglycaemia, masked hyperglycaemia, isolated nocturnal hyperglycaemia) can only be discussed after conducting adequately designed randomised clinical trials, which we would strongly encourage.

Conflict of interest

Authors have no conflicts of interest to declare.

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Da li kontinuirani monitoring glukoze možemo koristiti za postavljanje dijagnoze hiperglikemije belog mantila i potencijalno nekih drugih entiteta?

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SAŽETAK

Uvod. Od 1999. godine kontinuirano praćenje glukoze (engl. *continuous glucose monitoring* – CGM) koristi se za merenje koncentracije glukoze u intersticijskoj tečnosti. CGM je ključan za dobijanje informacija o profilu glikemije, njenoj varijabilnosti, procentu vremena u kojem je glikemija bila u željenom opsegu (engl. *time in range* – TIR), i procentu vremena provedenog iznad i ispod željenog opsega.

Diskusija. Campbell i saradnici su 1992. godine prvi opisali hiperglikemiju belog mantila. Oni su je definisali kao stanje kada bolesnik ima povišen nivo glukoze u krvi u ordinaciji i/ili laboratoriji i normalan nivo glukoze dobijen samomerenjem. Pre uvođenja CGM, hiperglikemija belog mantila je definisana visokim vrednostima glukoze u ordinaciji/laboratoriji i normalnim vrednostima glikemije dobijenih samomerenjem. Danas se može reći da pacijent ima hiperglikemiju belog mantila kada ima povišen nivo glukoze u ordinaciji i normalan nivo glikemije dobijen samomerenjem i/ili TIR iznad 70% na CGM. Otkrivanje hiperglikemije belog mantila je od ključnog značaja za terapijski pristup jer intenziviranje terapije samo na osnovu glikemije dobijene u ordinaciji/laboratoriji može dovesti do epizoda hipoglikemije i potencijalno smrtonosnog ishoda. Ako se uporedi sa arterijskom hipertenzijom i ambulantnim praćenjem krvnog pritiska, CGM može dovesti do otkrivanja nekih drugih entiteta: 1) maskirane hiperglikemije; 2) izolovane noćne hiperglikemije.

Zaključak. Čini se logičnim da se CGM može koristiti za dijagnostikovanje hiperglikemije belog mantila i eventualno nekih (novih) entiteta. O kliničkom značaju svih ovih entiteta može se raspravljati samo nakon sprovođenja adekvatno dizajniranih nasumičnih kliničkih ispitivanja.

Ključne reči: šećerna bolest, kontinuirani monitoring glukoze, hiperglikemija belog mantila, ambulatorni monitoring krvnog pritiska