

## Assessment of a Clinical Case for A Female Patient with Type 2 Diabetes Using the 2021 Consensus Report on Type 2 Diabetes Remission Discussions Sponsored by American Diabetes Association Based on GH-Method: math-physical medicine (No. 506)

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### Abstract

This 73-year-old female patient has suffered from type 2 diabetes (T2D), hypertension, and hyperlipidemia for over 20 years. She started taking Metformin in 1999 and ceased taking it on 1/7/2019. As of 4/3/2019, her HbA1C level was at 6.6%. Since 4/4/2019, she implemented a lifestyle management program which not only focuses on diet and exercise but also factors in sleep, stress, life routines and habits, as well as environmental factors.

In this article, the author applies the final conclusions from the American Diabetes Association (ADA) 2021 consensus report regarding "T2D Remission". For this clinical case, he analyzes the patient's present conditions to determine if she satisfies the criteria of "T2D remission" or not.

The defined criteria of "remission" include timespan of at least one year, HbA1C level less than 6.5%, fasting plasma glucose (FPG) level less than 126 mg/dL, and estimated HbA1C (eA1C) values based on the mean continuous glucose monitoring (CGM) glucose data less than 6.5%.

In conclusion, according to the ADA 2021 consensus report, this female patient is in "remission" for T2D. In summary, over the past year from 9/5/2020 to 9/5/2021, her average lab-A1C is 6.3%, mean CGM FPG value is 102 mg/dL, and CGM eAG is 5.7%.

First, the selected one year satisfies the timespan requirement cited in the 2021 consensus report. Her set of glucose data has been collected over ~3 years, after post-Metformin (started on 1/7/2019) and her initiation of lifestyle management program that began on 4/4/2019.

Second, all of her A1C values, both lab-tested and CGM eA1C, are less than 6.5% and her mean CGM FPG level is less than 126 mg/dL.

Finally, she keeps a regular routine with quarterly medical examinations to monitor various diabetes complications, including macro-vascular, micro-vascular, neural, and hormonal systems.

The author understands and agrees with the consensus report that diabetes is non-curable and at most is "controllable" or "partially reversible". Nevertheless, this female patient has also adopted a similar lifestyle improvement program as the author in order to deal with the root causes of her multiple metabolic disorders, particularly T2D, instead of suppressing the external symptoms of diabetes through medication intervention.

## Introduction

This 73-year-old female patient has suffered from type 2 diabetes (T2D), hypertension, and hyperlipidemia for over 20 years. She started taking Metformin in 1999 and ceased taking it on 1/7/2019. As of 4/3/2019, her HbA1C level was at 6.6%. Since 4/4/2019, she implemented a lifestyle management program which not only focuses on diet and exercise but also factors in sleep, stress, life routines and habits, as well as environmental factors.

In this article, the author applies the final conclusions from the American Diabetes Association (ADA) 2021 consensus report regarding “T2D Remission”. For this clinical case, he analyzes the patient’s present conditions to determine if she satisfies the criteria of “T2D remission” or not.

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## Methods

**MPM Background:** To learn more about his developed GH-Method: math-physical medicine (MPM) methodology, readers can read the following three papers selected from his ~500 published medical papers.

The first paper, No. 386 describes his MPM methodology in a general conceptual format. The second paper, No. 387 outlines the history of his personalized diabetes research, various application tools, and the differences between biochemical medicine (BCM) approach versus the MPM approach. The third paper, No. 397 depicts a general flow diagram containing ~10 key MPM research methods and different tools.

The consensus report of T2D remission: From 2009 to 2021, the ADA convened an international, multidisciplinary expert group. Representatives from the ADA, European Association for the Study of Diabetes, Diabetes UK, the Endocrine Society, and the Diabetes Surgery Summit, with one additional oncologist were included.

The following is a long excerpt from the “Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes” by Matthew C. Riddle, William T. Cefalu, Philip H. Evans, Hertzal C. Gerstein, Michael A. Nauck, William K. Oh, Amy E. Rothberg, Carel W. le Roux, Francesco Rubino, and other authors, published on August 30, 2021, in the *The Journal of Clinical Endocrinology & Metabolism*. The original paper has 6,328 words. The author considers this paper as a trove of knowledge; therefore, he has kept ~40% of its original words (2,500 words) in this excerpt for future access.

“Abstract: This group proposed “remission” as the most appropriate descriptive term, and HbA1C < 6.5% (48 mole/mol) measured at least 3 months after cessation of glucose-lowering pharmacotherapy as the usual diagnostic criterion.

Consensus Statement: The natural history of type 2 diabetes (T2D)

is clearly heterogeneous, with both genetic and environmental factors contributing to its pathogenesis and evolution. Typically, a genetic predisposition is present at birth but the hyperglycemia that defines diabetes appears only gradually and reaches diagnostic levels in adulthood. Environmental factors modulating expression of T2D include availability of various foods; opportunity for and participation in physical activity; stress related to family, work, or other influences; exposure to pollutants and toxins; and access to public health and medical resources.

T2D that has developed gradually and independent of these stimuli, but most often accompanying weight gain in midlife, can become easier to control or appear to remit following weight loss in some cases.

Significant behavioral changes—mainly related to nutrition and weight management—can lead to a return from overt hyperglycemia to nearly normal glucose levels for extended periods of time.

In 2009 a consensus statement initiated by the American Diabetes Association (ADA) addressed these issues. It suggested that “remission,” signifying “abatement or disappearance of the signs and symptoms,” be adopted as a descriptive term.

Three categories of remission were proposed.

(1) “Partial” remission was considered to occur when hyperglycemia below diagnostic thresholds for diabetes was maintained without active pharmacotherapy for at least 1 year. (2) “Complete” remission was described as normal glucose levels without pharmacotherapy for 1 year. (3) “Prolonged” remission could be described when a complete remission persisted for 5 years or more without pharmacotherapy.

A level of HbA1c <6.5% (<48 mmol/mol) and/or fasting plasma glucose (FPG) 100–125 mg/dL (5.6 to 6.9 mmol/L) were used to define a partial remission, while “normal” levels of HbA1c and FPG (<100 mg/dL [5.6 mmol/L]) were required for a complete remission.

To build upon this statement and subsequent publications in the context of more recent experience, the ADA convened an international, multidisciplinary expert group. Representatives from the American Diabetes Association, European Association for the Study of Diabetes, Diabetes UK, the Endocrine Society, and the Diabetes Surgery Summit were included. For another perspective, an oncologist was also part of the expert group. This group met three times in person and conducted additional electronic exchanges between February 2019 and September 2020. The following is a summary of these discussions and conclusions derived from them.

## Optimal Terminology

In T2D, the terms resolution, reversal, remission, and cure each have been used to describe a favorable outcome of interventions resulting in a disease-free status. In agreement with the prior consensus group’s conclusions, this expert panel concluded that diabetes remission is the most appropriate term. Remission is a term widely used in the field of oncology (18), defined as a decrease in or disappearance of signs and symptoms of cancer. Diabetes

is defined by hyperglycemia, which exists on a continuum. One reason for this decision was that the underlying pathophysiology of T2D, including both deficiency of insulin and resistance to insulin's actions, as well as other abnormalities, is rarely completely normalized by interventions. In addition, any criterion for identifying a remission of diabetes will necessarily be arbitrary, a point on a continuum of glycemic levels. A single definition of remission based on glycemic measurements was thought more likely to be helpful. The term reversal is used to describe the process of returning to glucose levels below those diagnostic of diabetes, but it should not be equated with the state of remission.

#### ***Glycemic Criteria for Diagnosing Remission of T2D***

Measures widely used for diagnosis or glycemic management of T2D include HbA1c, FPG, 2-h plasma glucose after an oral glucose challenge, and mean daily glucose as measured by continuous glucose monitoring (CGM). The group favored HbA1c below the level currently used for initial diagnosis of diabetes, 6.5% (48 mmol/mol), and remaining at that level for at least 3 months without continuation of the usual antihyperglycemic agents as the main defining measurement. However, a number of factors can affect HbA1c measurements, including a variant hemoglobin, differing rates of glycation, or alterations of erythrocyte survival that can occur in a variety of disease states. Information on which methods are affected by variant hemoglobins can be found at <http://ngsp.org/interf.asp>. Thus, in some people a normal HbA1c value may be present when glucose is actually elevated, or HbA1c may be high when mean glucose is normal. In settings where HbA1c may be unreliable, measurement of 24-h mean glucose concentrations by CGM has been proposed as an alternative. A glycated hemoglobin value calculated as equivalent to the observed mean glucose by CGM has been termed the estimated HbA1c (eA1C) (25) or most recently a glucose management indicator (GMI) (26). In cases where the accuracy of HbA1c values is uncertain, CGM can be used to assess the correlation between mean glucose and HbA1c and identify patterns outside the usual range of normal (27, 28).

Considering all alternatives, the group strongly favored use of HbA1c < 6.5% (48 mmol/mol) as generally reliable and the simplest and most widely understood defining criterion under usual circumstances. In some circumstances, an eA1C or GMI < 6.5% can be considered an equivalent criterion.

#### ***Can Remission Be Diagnosed While Glucose-Lowering Drugs Are Being Used?***

Diabetes remission may be achieved by a change of lifestyle, other medical or surgical interventions, or, as is often the case, a combination of these approaches.

Alterations of lifestyle involving day-to-day routines related to nutrition and physical activity have health effects that extend well

beyond those related to diabetes. Moreover, the possibility of not only achieving diabetes remission but also generally improving health status may have motivated the individual to make these changes in the first place.

Whether a remission can be diagnosed in the setting of ongoing pharmacotherapy is a more complex question. If antihyperglycemic drug therapy continues, it is not possible to discern whether a drug-independent remission has occurred. A diagnosis of remission can only be made after all glucose-lowering agents have been withheld for an interval that is sufficient both to allow waning of the drug's effects and to assess the effect of the absence of drugs on HbA1c values.

This is a controversial area, with arguments both for and against. In favor of pharmacotherapy to prevent emergence or re-emergence of overt diabetes is the possibility of safely and inexpensively eliminating a period of undiagnosed yet harmful hyperglycemia (30). On the other side is the argument that protection against  $\beta$ -cell deterioration by pharmacotherapy has yet to be convincingly proven and preventive intervention has known costs and potential risks.

#### ***Temporal Aspects of Diagnosing Remission***

When intervention in T2D is by pharmacotherapy or surgery, the time of initiation is easily determined, and the clinical effects are rapidly apparent (Table 1). When intervention is by alteration of lifestyle, the onset of benefit can be slower, and up to 6 months may be required for stabilization of the effect. A further temporal factor is the approximately 3 months needed for an effective intervention to be entirely reflected by the change of HbA1c, which reflects mean glucose over a period of several months. Considering these factors, an interval of at least 6 months after initiation of a lifestyle intervention is needed before testing of HbA1c can reliably evaluate the response. After a more rapidly effective surgical intervention, an interval of at least 3 months is required while the HbA1c value stabilizes. When the intervention is with temporary pharmacotherapy, or when a lifestyle or metabolic surgery intervention is added to prior pharmacotherapy, an interval of at least 3 months after cessation of any glucose-lowering agent is required. With all interventions leading to remission, subsequent measurements of HbA1c not more often than every 3 months nor less frequent than yearly are advised to confirm continuation of the remission. In contrast to HbA1c, FPG or eA1C derived from CGM can stabilize at a shorter time after initiation of an intervention, or increase more rapidly if glycemic control worsens later on. When these measurements of glucose are substituted for HbA1c, they can be collected sooner after the intervention and more frequently thereafter, but because they are more variable, a value consistent with onset or loss of a remission should be confirmed by a repeated measurement.

**Table 1: Interventions and Temporal Factors in Determining Remission of T2D**

Intervention	Interval before testing of HbA1c can reliably evaluate the response	Subsequent measurements of HbA1c to document continuation of a remission
Note: Documentation of remission should include a measurement of HbA1c just prior to intervention		
Pharmacotherapy	At least 3 months after cessation of this intervention	Not more often than every 3 months nor less frequent than yearly
Surgery	At least 3 months after the procedure and 3 months after cessation of any pharmacotherapy	

### ***Physiologic Considerations Regarding Remissions Following Intervention With Pharmacotherapy, Lifestyle, or Metabolic Surgery***

When a remission is documented after temporary use of glucose-lowering agents, the direct effects of pharmacotherapy do not persist. Reversal of the adverse effects of poor metabolic control (32) on insulin secretion and action may establish a remission, but other underlying abnormalities persist and the duration of the remission is quite variable. In contrast, when a persistent change of lifestyle leads to remission, the change in food intake, physical activity, and management of stress and environmental factors can favorably alter insulin secretion and action for long periods of time. In this setting, long-term remissions are possible, but not assured. Partial regain of weight can occur, and continuing decline of  $\beta$ -cell capacity may contribute to rising levels of glucose over time.

### ***Ongoing Monitoring***

A remission is a state in which diabetes is not present but which nonetheless requires continued observation because hyperglycemia frequently recurs. Weight gain, stress from other forms of illness, and continuing decline of  $\beta$ -cell function can all lead to recurrence of T2D. Testing of HbA1c or another measure of glycemic control should be performed no less often than yearly. Ongoing attention to maintenance of a healthful lifestyle is needed. The metabolic memory, or legacy effect, is relevant in this setting. These terms describe the persisting harmful effects of prior hyperglycemia in various tissues. Even after a remission, the classic complications of diabetes—including retinopathy, nephropathy, neuropathy, and enhanced risk of cardiovascular disease—can still occur. Hence, people in remission from diabetes should be advised to have regular retinal screening, tests of renal function, foot evaluation, and measurement of blood pressure and weight in addition to ongoing monitoring of HbA1c. At present, there is no long-term evidence indicating that any of the usually recommended assessments for complications can safely be discontinued. Individuals who are in remission should be advised to remain under active medical observation including regular check-ups.

In addition to continued gradual progression of established complications of T2D, there is another risk potentially associated with a remission. This is the possibility of an abrupt worsening of microvascular disease following a rapid reduction of glucose levels after a long period of hyperglycemia. In particular, when poor glycemic control is present together with retinopathy beyond

the presence of microaneurysms, rapid reduction of glucose levels should be avoided and retinal screening repeated if a rapid decline in blood glucose is observed.

### ***Further Questions and Unmet Needs***

#### ***Validation of Using 6.5% HbA1c as the Defining Measurement***

The relative effectiveness of using 6.5% HbA1c (48 mmol/mol) as the cut point for diagnosis of remission, as opposed to 6.0% HbA1c (42 mmol/mol), HbA1c 5.7% (39 mmol/mol), or some other level, in predicting risk of relapse or of microvascular or cardiovascular complications should be evaluated. The use of CGM-derived data to adjust HbA1c target ranges for identifying glycemic remission should be further explored. Use of CGM-derived average glucose judged equivalent to HbA1c <6.5% (<48 mmol/mol) or use of FPG < 7.0 mmol/L (<126 mg/dL) instead of HbA1c could be studied.

#### ***Validation of the Timing of Glycemic Measurements***

Less frequent testing of HbA1c might be possible without altering predictive efficiency. For example, routine measurements at 6 months and 12 months might be sufficient to identify remission and risk of relapse in the short term.

#### ***Evaluation of Nonglycemic Measures During Remission***

Improved glycemic control is not the only aspect of metabolism that may affect long-term outcomes. For example, circulating lipoprotein profiles, peripheral and visceral adiposity, and intracellular fat deposition in the liver and other tissues may all be relevant effects accompanying—or possibly separate from—glycemic remission and could be evaluated.

#### ***Research on Duration of Remission***

The expected duration of a remission induced by various interventions is still not well defined, and factors associated with relapse from remission should be examined more fully.

#### ***Documentation of Long-term Outcomes After Remission***

Long-term effects of remission on mortality, cardiovascular events, functional capacity, and quality of life are unknown. Metabolic and clinical factors related to these outcomes during remission are poorly understood and could be defined.

### ***Conclusions***

A return to normal or nearly normal glucose levels in patients with typical T2D can sometimes be attained by using current and



emerging forms of medical or lifestyle interventions or metabolic surgery. The frequency of sustained metabolic improvement in this setting, its likely duration, and its effect on subsequent medical outcomes remain unclear. To facilitate clinical decisions, data collection, and research regarding outcomes, more clear terminology describing such improvement is needed. On the basis of our discussions, we propose the following:

1. The term used to describe a sustained metabolic improvement in T2D to nearly normal levels should be remission of diabetes.
2. Remission should be defined as a return of HbA1c to  $< 6.5\%$  ( $< 48$  mmol/mol) that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy.
3. When HbA1c is determined to be an unreliable marker of chronic glycemic control, FPG  $< 126$  mg/dL ( $< 7.0$  mmol/L) or eA1C  $< 6.5\%$  calculated from CGM values can be used as alternate criteria.
4. Testing of HbA1c to document a remission should be performed just prior to an intervention and no sooner than 3 months after initiation of the intervention and withdrawal of any glucose-lowering pharmacotherapy.
5. Subsequent testing to determine long-term maintenance of a remission should be done at least yearly thereafter, together with the testing routinely recommended for potential complications of diabetes.
6. Research based on the terminology and definitions outlined in the present statement is needed to determine the frequency, duration, and effects on short- and long-term medical outcomes of remissions of T2D using available interventions.

This Consensus Report is jointly published in The Journal of Clinical Endocrinology & Metabolism, published by Oxford University Press on behalf of the Endocrine Society; Diabetologia, published by Springer-Verlag, GmbH, on behalf of the European Association for the Study of Diabetes; Diabetic Medicine, published by Wiley on behalf of Diabetes UK; and Diabetes Care, published by the American Diabetes Association.

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#### *The author's learned key-points from the consensus report*

After reading the report five times and absorbing its excellent

content, the author attempts to re-write certain selected phrases into the conclusions of this paper. He has summarized the ADA 2021 consensus points, while excluding some of the ADA 2019 consensus points, such as the prolonged remission, etc. His only intervention is through a stringent and persistent 7 to 10-year long lifestyle management program, without any medications or surgeries.

#### *Listed below are six conclusions regarding the “remission” of his T2D:*

1. The sustained metabolic improvement in T2D to nearly normal levels, HbA1C  $< 6.5\%$ , FPG  $< 126$  mg/dL, and eA1C  $< 6.5\%$  should be considered as “remission” of diabetes.
2. A return of HbA1c to  $< 6.5\%$  that occurs following a lifestyle improvement intervention which persists for at least 3 months in the absence of usual diabetes medications.
3. In addition to HbA1c (when it is determined to be an unreliable or questionable biomarker of chronic glycemic control), FPG  $< 126$  mg/dL or eA1C  $< 6.5\%$  calculated from CGM values are also used as alternate or additional criteria.
4. Testing of HbA1c should be performed just prior to an intervention and no sooner than six months after withdrawal of any glucose pharmacotherapy.
5. Subsequent testing to determine long-term maintenance of a remission are done near quarterly thereafter, together with other necessary tests routinely for other potential complications of diabetes, such as cardiovascular disease (CVD), chronic kidney disease (CKD), diabetic retinopathy (DR), neuropathy, hypothyroidism, etc.
6. This research work based on the terminology and definitions outlined in the present statement is needed to determine the frequency, duration, and effects on short-term and long-term medical outcomes of remissions of T2D. However, in this particular clinical case of a female T2D patient, she uses the lifestyle intervention exclusively and does not adopt any medical intervention related to medication or surgery.

The following data analyses and their results are based on these six conclusions.

#### **Results**

Figure 1 depicts his HbA1C situations of the selected year from 9/5/2020 to 9/5/2021. The following data table lists his average values during this period:

**Lab-tested A1C (right table)**

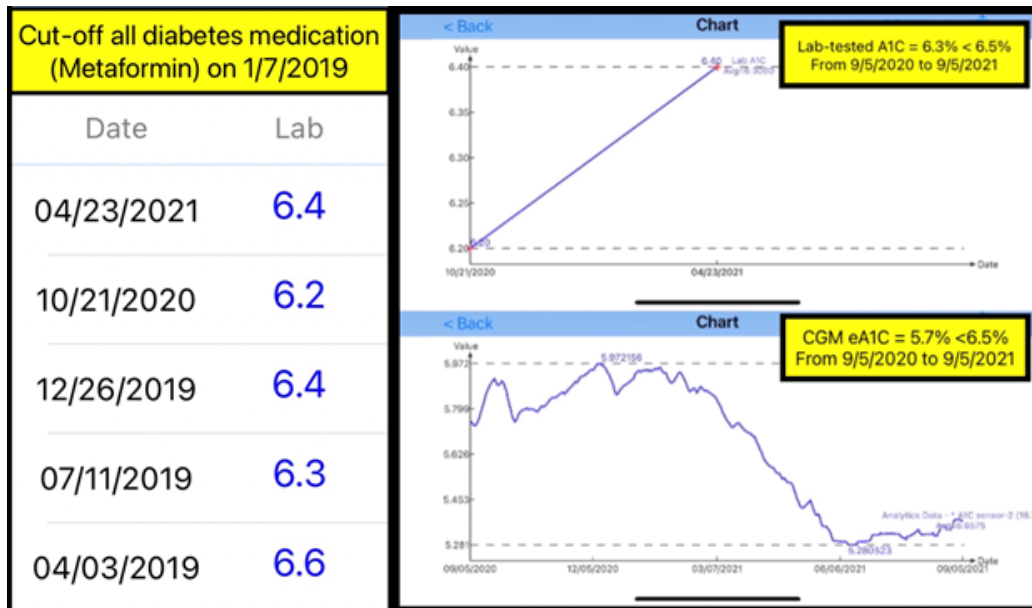
**= 6.3% (7/11/19-4/23/21)**

**Lab-tested A1C (upper-left diagram)**

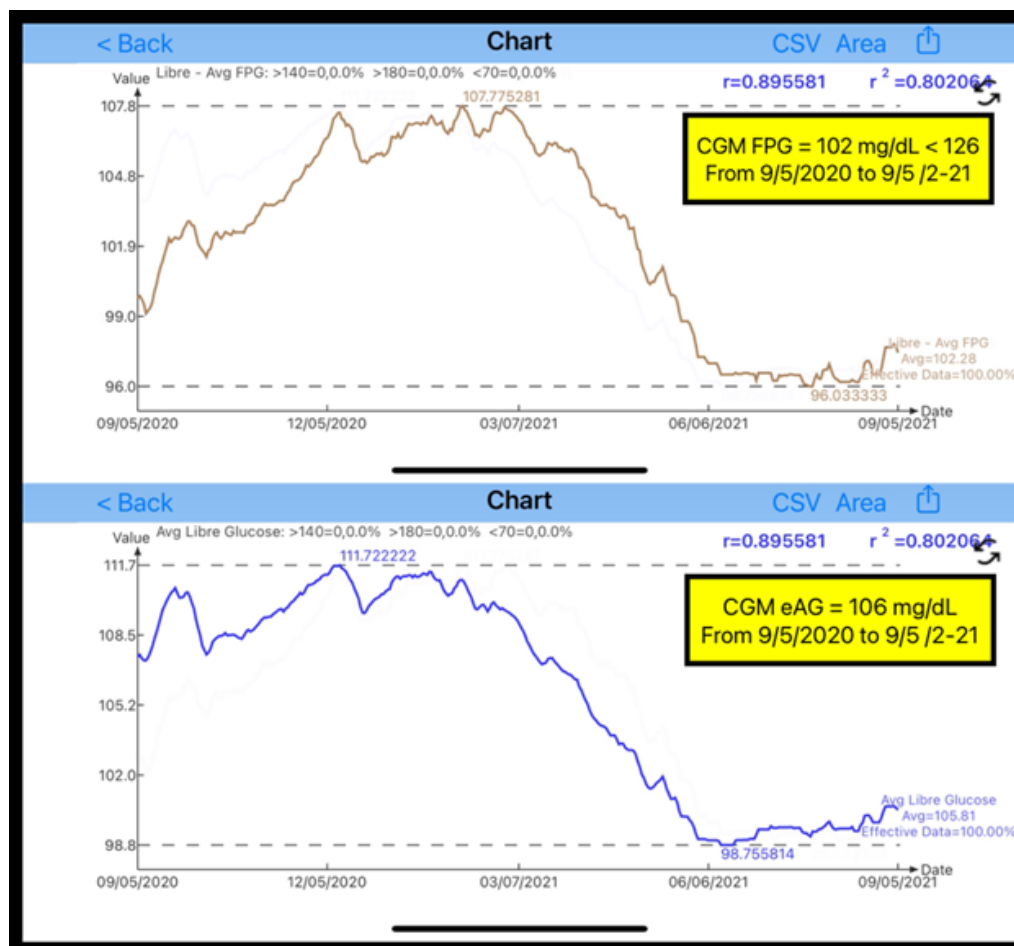
**= 6.3% (9/5/20-9/5/21)**

**CGM eA1C (lower-left diagram)**

**= 5.7% (9/5/20-9/5/21)**



**Figure 1:** HbA1C comparisons for Lab-tested A1C data during a 3-year period (4/3/19-9/5/21), and Lab-tested A1C with CGM eA1C during 1-year period (9/5/20-9/5/21)



**Figure 2:** Remission examination using FPG, and CGM eA1C which is based on (CGM eAG / 18.7) for the period of 9/5/2020-9/5/2021

Figure 2 illustrates his two mean CGM glucoses, CGM FPG = 102 mg/dL and CGM eAG = 106 mg/dL.

Again, his CGM eA1C is calculated using the following formula:

$$CGM\ eA1C = CGM\ eAG / 18.7$$

The objective of this study is to determine whether the female patient's T2D situation, over the past one year and at present time, belongs to a "remission" state or not. The selected timespan of all judgmental data are from 9/5/2010 to 9/5/2021. The author used three criteria that includes the lab-HbA1C, FPG, and CGM eA1C to make his final judgement for her "T2D remission" status.

The following table lists her results:

*Lab-tested HbA1C = 6.3% (<6.5%)*  
*CGM FPG = 102 mg/dL (<126)*  
*CGM eA1C = 5.7% (<6.5%)*

*Based on the above findings, the female T2D patient indeed belongs to a "remission" state at present time.*

## Conclusion

*In conclusion, according to the ADA 2021 consensus report, this female patient is in "remission" for T2D.* In summary, over the past year from 9/5/2020 to 9/5/2021, her average lab-A1C is 6.3%, mean CGM FPG value is 102 mg/dL, and CGM eAG is 5.7%.

First, the selected one year satisfies the timespan requirement cited in the 2021 consensus report. Her set of glucose data has been collected over the past ~3 years, after post-Metformin (started on 1/7/2019) and her initiation of lifestyle management program began on 4/4/2019.

Second, all of her A1C values, both lab-tested and CGM eA1C, are less than 6.5% and her mean CGM FPG level is less than 126 mg/dL.

Finally, she keeps a regular routine with quarterly medical examinations to monitor various diabetes complications, including macro-vascular, micro-vascular, neural, and hormonal systems.

*The author understands and agrees with the consensus report that diabetes is non-curable and at most is "controllable" or "partially reversible". Nevertheless, this female patient has also adopted a similar lifestyle improvement program as the author in order to deal with the root causes of her multiple metabolic disorders, particularly T2D, instead of suppressing the external symptoms of diabetes through medication intervention.*

## References

1. Matthew C Riddle, William T Cefalu, Philip H Evans, Hertzel C Gerstein, Michael A Nauck, et al. (2021) "Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes". Diabetes Care 44: 2438-2444.

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