ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2024 September 15; 15(9): 1829-2001

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 15 Number 9 September 15, 2024

World Journal of Diabetes

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Contents

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Contents

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Md. Shahidul Islam, Lu Cai, Michael Horowitz

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https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE
September 15, 2024

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World Journal of Diabetes

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World J Diabetes 2024 September 15; 15(9): 1858-1861

DOI: 10.4239/wjd.v15.i9.1858

ISSN 1948-9358 (online)

FIELD OF VISION

Rapid correction of chronic hyperglycemia and bone remodeling, warning against overdoing

Dured Dardari, Beatrice Segurens

Specialty type: Endocrinology and metabolism

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A

Novelty: Grade A

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Wu ZJ

Received: January 29, 2024

Revised: June 4, 2024

Accepted: July 2, 2024

Published online: September 15, 2024

Processing time: 210 Days and 23.1 Hours

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Abstract

It is widely recognized that chronic hyperglycemia decreases bone quality, although little is known about the impact of the rapid correction of chronic hyperglycemia on the quality of bone remodeling. This spotlight article explores this correlation by focusing on the stages of bone remodeling linked to glucose levels.

Key Words: Bone remodeling; Chronic hyperglycemia; Intensive hyperglycemia treatment; Diabetes complication; Rapid correction of hyperglycemia

Core Tip: The protein osteocalcin involved in bone remodeling is affected by glucose metabolism and variation. Osteoprotegerin and receptor activator of NF-kB ligand also involved in bone modeling are equally sensitive to glucose variation. Bone remodeling is impaired when glucose levels are reduced and only not only when the blood glucose threshold is exceeded.

Citation: Dardari D, Segurens B. Rapid correction of chronic hyperglycemia and bone remodeling, warning against overdoing. *World J Diabetes* 2024; 15(9): 1858-1861

URL: https://www.wjgnet.com/1948-9358/full/v15/i9/1858.htm

DOI: https://dx.doi.org/10.4239/wjd.v15.i9.1858

INTRODUCTION

The protein osteocalcin (OC) involved in bone remodeling is affected by glucose metabolism and variation.

Osteoprotegerin (OPG) and receptor activator of NF-kB ligand also involved in bone modeling are equally sensitive to glucose variation.

Bone remodeling is impaired when glucose levels are reduced and only not only when the blood glucose threshold is exceeded.

HOW RAPID CORRECTION OF CHRONIC HYPERGLYCAEMIA AFFECTS BONE REMODELING

It has been suggested that bone contributes to the overall physiology of the body as an endocrine hormone[1]. To maintain its activity, bone is constantly remodeled by osteoblasts (OB) and osteoclasts[2]. During the various stages of OB differentiation, different biomarkers such as the OC are involved. Secreted by OB, OC is a bone component and biomarker of bone mineralization. Nevertheless, there are several shortcomings regarding the idea of OC as an endocrine hormone[3]. OC increases the insulin sensitivity of the target organs by stimulating glucose uptake by the muscles, increasing adiponectin production by adipose tissue, reducing lipid accumulation and inflammation in the liver, and promoting insulin secretion by the pancreas. The latter action is directly related to glucose metabolism[3]. This demonstrates the link between bone remodeling and glucose metabolism *via* the impact of glucose metabolism on OC. Patients with hyperglycemia have low levels of OC[4,5]. If hyperglycemia is corrected rapidly, the level of OC will also rise, thus accelerating the bone remodeling process.

Furthermore OPG is a soluble glycoprotein produced mainly by OB, which inhibits osteoclast genesis by preventing the binding of the receptor activator of nuclear factor-κB ligand (RANKL) to its receptor RANK[6]. However, RANKL is an osteoclast differentiation factor produced by OB, which triggers osteoclast genesis by binding to RANK, a membrane receptor expressed by osteoclast precursors[7]. In a study[8], OPG was inhibited by the correction of hyperglycemia, twenty-two patients with newly diagnosed type 1 diabetes were treated with insulin, with a drop in HbA1c from 11.1% (98 mmol/mol) at diagnosis to 6.2% (44 mmol/mol) after 6 months. The plasma OPG level in the patients before treatment was 3.1 ng/L, and after 6 months treatment it was decreased to 2.6 ng/L ($P < 0.001$) but was still higher than in 28 healthy controls (2.1 ng/L). Elevated levels of OPG have previously been shown in patients with both type 1 and type 2 diabetes and have been associated to hyperglycemia[9,10]. We would therefore conclude that rapidly reducing hyperglycaemia inhibits OPG and increases RANKL.

In a different vein, OB use glucose during differentiation *via* both oxidative phosphorylation and aerobic glycolysis [11]. However, it is also known that hyperglycemia plays a role in OB differentiation, whereas OB have insulin receptors. The binding of insulin to its OB receptor induces bone formation and the production of OC as well as a decrease in the expression of OPG[11]. It can therefore be concluded that the lack of insulin induced by hyperglycemia reduces the OB differentiation. However, insulin can stimulate the secretion of OC. OB that produce proteins also express an insulin receptor. Following its binding to its receptor, insulin not only induces bone formation but also decreases the expression of OPG, which inhibits the differentiation and activation of osteoclasts, the cells responsible for the resorption of the bone matrix.

Glucose levels, glucose metabolism, and insulin seem play a role in every stage of bone remodeling: They activate OC, reduce OPG, and differentiate OB. While previous studies have focused on the role played by hyperglycemia in the disruption and imbalance of bone remodeling, few have focused on the possible impact of hyperglycemia on bone remodeling, as presented in Figure 1, which illustrates how the correction of hyperglycemia impacts bone remodeling. However, in our focus we have not put the spotlight on the role of RANK due to the lack of studies on the topic.

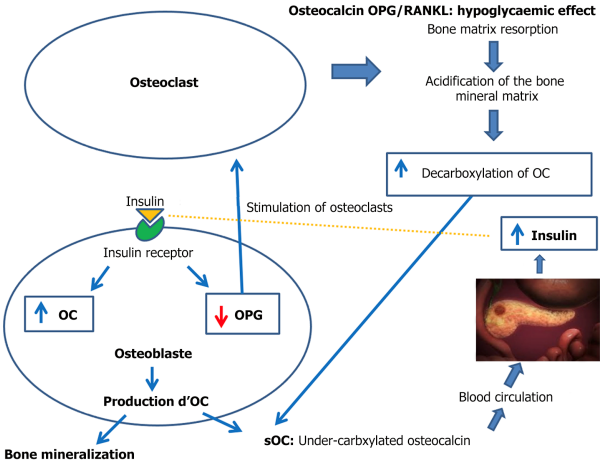

Figure 1 How the correction of hyperglycemia impacts bone remodeling. OC: Osteocalcin; OPG: Osteoprotegerin; OB: Osteoblasts; RANKL: Receptor

activator of nuclear factor-κB ligand.

CONCLUSION

This spotlight highlights the impact of the rapid correction of hyperglycemia on bone remodeling. In the literature, this impact has rarely been described. It has been suggested that certain profiles of patients living with chronic hyperglycemia should undergo a bone health assessment prior to the correction of chronic hyperglycemia. For example, simple bone densitometry can guide physicians or give clues about the state of the bone structure. This type of low-cost exploration can reduce the risk of bone diseases whose mechanism is linked to the alteration of bone modeling such as osteoporosis or Charcot's neuroarthropathy[12]. Finally, it is possible that the anti-RANKL therapies used in certain diseases such as osteoporosis could be a means of preventing the perturbation of bone modelling for people living with chronic hyperglycaemia and for whom a rapid reduction in this hyperglycaemia is planned in a short-term perspective.

ACKNOWLEDGEMENTS

The authors acknowledge Natacha Vitrat Gip Genopole Genopole Campus 1 20, Rue Henri Desbruères F-91030 Evry, FRANCE.

FOOTNOTES

Author contributions: Dardari D and Segurens B wrote the protocol, produced the statistics, collected the data, wrote and reviewed the manuscript; Dardari D and Segurens B are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; All authors approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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S-Editor: Li L
L-Editor: A
P-Editor: Cai YX

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