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Fibroblast growth factor 23 in acute burn patients: Novel insights from an intact-form assay

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ABSTRACT

Introduction: Fibroblast growth factor 23 (FGF23) is a key regulator in phosphate and vitamin D metabolism When measured with c-terminal assay, it has been shown to be increased following burn. Progress in understanding FGF23 physiology has emphasized the importance of assessing the intact form of FGF23.

Methods: The present cohort study is a complementary analysis of a previously published work. Patients >18 years, admitted within 24 h after injury with burn surface area (BSA) >10% were included. C-terminal (c-term) and intact (i) FGF23 assay were performed at admission and every week during 4 weeks of follow-up. Inflammation and iron status were assessed at the same time points.

Results: Twenty patients were initially included and 12 were followed until day 28. The c-term FGF23 tended to gradually increase during the 4 weeks of follow-up while iFGF23 was quite stable into normal ranges. Iron status showed a typical inflammatory profile. C-term FGF23 was significantly positively correlated with c-reactive protein (CRP) and negatively correlated with iron levels. iFGF23 was not correlated with CRP or iron.

Conclusion: FGF23 status following burn is characterized by a dissociation between c-term FGF23 and iFGF23. The hypothesis of an increased cleavage may be raised. Respective role of inflammation and iron levels in such deregulation need to be specified. Both c-term and intact assays should be performed in further studies aiming to increase knowledge on FGF23 regulation and effects in burn patients.

1. Introduction

Fibroblast growth factor 23 (FGF23) is a bone derived hormone that is implicated in phosphate (P) and vitamin D (VD) regulation. It is produced mainly by osteocytes, but also by osteoblasts, osteoprogenitor cells, cementoblasts, odontoblasts, and chondrocytes [1]. FGF23 binds the FGF receptor – αKlotho complex. FGF receptor (FGFR) is broadly expressed, while the co-receptor αKlotho is expressed only in a few

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tissues including kidney, parathyroid or pituitary. The primary target of FGF23 is the kidney where it regulates genes of 2a sodium/phosphate cotransporter and 1α-hydroxylase, leading to phosphate excretion and inhibition of 25 hydroxyvitamin D (25(OH)-D) hydroxylation [2]. In addition, FGF23 is able to stimulate expression of the vitamin D 24-hydroxylase, thus increasing 25(OH)-D and 1,25 dihydroxyvitamin D ($1,25(OH)_2$-D) inactivation. The principal regulators of FGF23 are thought to be P and $1,25(OH)_2$-D levels. However, the regulation of FGF23 expression is complex and still incompletely understood.

Burn induces significant physiologic changes involving cardiovascular system, immune system, metabolism or electrolyte balance. In particular, severe hypophosphatemia is frequently observed in acute burn patients. The exact mechanism of this phenomenon is not fully known but probably involves various factors such as type and quantity of fluid resuscitation, acid-base disturbances, electrolytes imbalances catecholamines or exudative losses [3,4]. Hypophosphatemia may have significant consequences in term of cellular membrane integrity or energy metabolism. From another point of view, burn has repercussions on VD synthesis due to skin damage and, later, strategies to prevent abnormal scarring following burn healing (sunlight eviction and pressure garments). Furthermore, alterations of VD physiology and metabolism may be suspected in severe burn patients who are thus at high risk of VD deficiency [5]. Given its role in P and VD metabolism, it may be therefore relevant to focus on FGF23 in the particular context of burn.

In a previous work [6], we studied blood levels of c-terminal FGF23 (c-term FGF23) in adult burn patients during acute care. However, FGF23 status may be even more complex than reported, due to the processing of the FGF23 protein (Fig. 1). FGF23 is initially expressed as a 251-amino acid protein. The signal peptide (the 24 first amino acids) is then cleaved off to produce the mature protein, which is considered biologically active. This last molecule is secreted intact or cleaved within bone cells. The proteolytic cleavage site is located between amino acid 179 and 180 (the RXXR region) and is thought to be recognized by subtilisin-like protein convertases such as furin. Cleavage results in production of the two inactive N-terminal and C-terminal fragments. Glycosylation of FGF23 by polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) seems to prevent cleavage [2].

There are currently two strategies to quantify circulating FGF23 concentrations, detecting different hormone's forms. The c-term enzyme-linked immunosorbent assay (ELISA) recognizes both intact hormone and C-terminal fragment, while the intact ELISA only recognizes the full-length mature hormone (Fig. 1).

In the past few years, knowledge about FGF23 physiology, processing and regulation has improved. Particularly, impact of iron deficiency on FGF23 production and cleavage has been cited in different clinical conditions [2,7]. Moreover, new commercial intact assays were recently available at more affordable terms. Using frozen blood samples from adult burn patients included in our previous study [6], the objective of the present analyses was to explore intact FGF23 in conjunction with iron and inflammation status. Indeed, data about intact FGF23 have not yet been reported in the specific context of burn.

2. Methods

This cohort study was conducted from March 2012 to January 2013 in a 6-bed burn unit after approval by the local Ethics Committee of our University Hospital (Ref B707201213417, 6th March 2012). Informed consent was obtained from the patients or their relatives prior to enrolment.

The details of the study design have been previously published [6]. In summary, Caucasian patients over 18 years, with a burn surface area (BSA) greater than 10% and admitted within the first 24 h following injury were included. Pregnancy, renal or liver failure, prior vitamin D substitution were considered exclusion criteria. They benefited from local standard monitoring and care procedures in term of fluid resuscitation, nutrition and surgery. They daily received vitamin D3 (cholecalciferol, VD3) from nutrition and multivitamin complex supplementation, reaching a daily dose of 600 to 800 UI. Patients did not receive any iron supplementation. Iron intakes ranged around 20 mg per day, provided by hospital made menu, enteral nutrition (Fresubin® HP Energy, Fresenius-Kabi, Germany), oral nutritional supplements

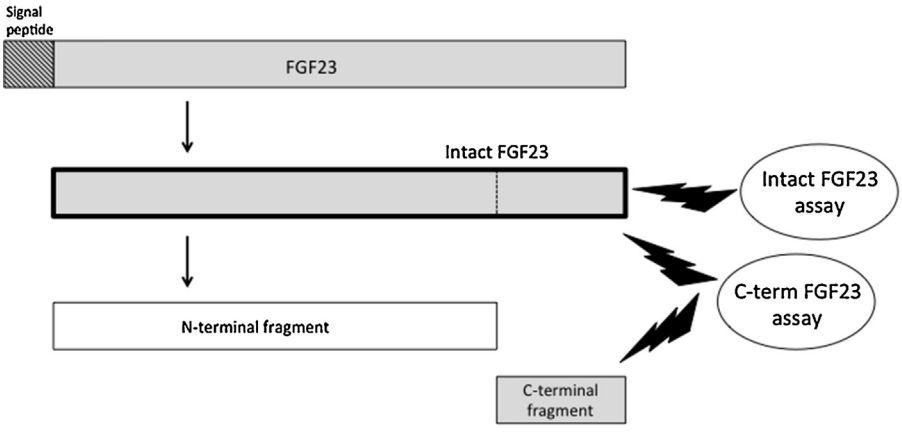

Fig. 1 – Processing of FGF23 protein.