

## OBESITY AND MAGNESIUM DEFICIENCY: IS OXIDATIVE STRESS INVOLVED?

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### Abstract

*Obesity – the “epidemic” of our century, an energy-rich condition, is associated with a chronic inflammatory reaction in adipose tissue. There is a controlled interaction between metabolic and immune systems in the over or under-nutrition states. Magnesium deficiency contributes to immune stress response and the oxidative stress is its consequence. There are similar pathways associated with the development of obesity-induced inflammation and magnesium deficiency in this state. The pivotal role is supported by the stress response.*

**Keywords:** obesity, magnesium deficiency, inflammation, oxidative stress.

### OBEZITATEA ȘI DEFICIENȚA DE MAGNEZIU: ESTE IMPLICAT STRESUL OXIDATIV ?

#### Rezumat

*Obezitatea – maladia secolului, se asociază cu o reacție inflamatorie cronică în țesutul adipos. Există o interacțiune între sistemul metabolic și imun atât la pacienții obezi, cât și subnutriți. Deficitul de magneziu contribuie la generarea răspunsului de stres imun, consecința acestuia fiind apariția stresului oxidativ. Există mecanisme asemănătoare cu apariția inflamației induse de obezitate și deficitul de magneziu prezent în acest context. Rolul cheie este deținut de către stresul oxidativ.*

**Cuvinte cheie:** obezitate, hipomagnezie, inflamație, stres oxidativ.

### INTRODUCTION

Obesity represents the most prevalent nutritional problem, with growing rates of morbidity and mortality in the latest decades. The ongoing rise in obesity reflects changes in lifestyle but the genetic background is also involved [1,2].

Magnesium plays a crucial role in several fundamental cellular reactions. A large number of clinical disorders have been found to be associated with magnesium deficiency [3,4]. One of these disorders is obesity. The common link between obesity and magnesium deficiency may be sustained by the inflammatory response which is the major origin of the oxidative stress (OS).

The implication of OS generated by magnesium deficiency – induced inflammation in obesity state will be discussed in the subsequent paragraphs.

### OBESITY – A LOW-GRADE INFLAMMATORY DISEASE

Chronic stress is known to be a threat to the metabolic homeostasis and can lead to complications caused by the stressor and the delay of the adaptive response [5]. Obesity impairs metabolic homeostasis and elicits stress response [6]. The associated secretion of proinflammatory cytokines by the adipose tissue may act as an additional chronic stimulus which maintains the chronic stress reactions.

The inflammatory status in obesity is indicated by the presence of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) in the adipose tissue. This was a major discovery and contributed to a better understanding of the relation obesity – inflammation [7,8].

Adipose tissue is the site of secretion for several proinflammatory factors such as interleukine 6 (IL-6), C – reactive protein, serum amyloid A, plasminogen activator inhibitor – 1 [9,10]. In obese states, adipose tissue is infiltrated by macrophages and there is a shift between alternatively activated M<sub>2</sub> type to the classically activated M<sub>1</sub> type [11,12]. This shift results in changes in secreted cytokines from anti – inflammatory M<sub>2</sub> to proinflammatory

Articol intrat la redacție în data de: 18.08.2010

Primit sub formă revizuită în data de: 05.10.2010

Acceptat în data de: 12.10.2010

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M<sub>1</sub> [13]. The secretion of proinflammatory factors by adipose tissue and their regulation sustain the hypothesis of a low – grade inflammation during obesity.

In addition to the proinflammatory cytokines that are expressed in fat, specific factors are produced from adipocytes and are generally named adipokines. In 1994 Zhang et al isolated a hormone, the leptin, from the adipose tissue [14]. This elucidated the fact that adipose tissue is not only a lipid storage, but is involved in the regulation of energy homeostasis. The principal function of leptin is to signal the energy state of the organism. In obesity, there is a leptin resistance that promotes the vicious circle of regulation of energy homeostasis. The direct contribution of leptin resistance in the development of obesity – inflammation has not yet been elucidated [15,16]. Circulating levels of adipokines in humans reflect the degree of their adiposity.

Obesity is a low – grade inflammatory disease, and the expression of proinflammatory cytokines is the first pathway in the generation of reactive oxygen species. The exposure to stress conditions in obesity is a result of metabolic overload [17]. Mitochondria and endoplasmic reticulum are the most sensitive organelles to metabolic stressors. The development of oxidative stress in adipose tissue activates several kinases [18].

The proinflammatory mediators, intracellular processes and their pathways are linking obesity to inflammation and therefore to intense reactions of oxidative stress.

### MAGNESIUM DEFICIENCY INDUCED INFLAMMATION-OXIDATIVE STRESS

Several lines of evidence support the role of inflammation in magnesium deficiency states. The following pathways should be considered [19,20,21]:

- Cellular entry of calcium and priming of phagocytic cells;
- Opening of calcium channels and activation of specific receptors;
- Release of neurotransmitters: substance P;
- Membrane oxidation and activation of nuclear factor kappa B (NFkB).

The inflammatory response is probably secondary to a modification in the extracellular magnesium level because of the decline in plasma magnesium. The intracellular level of magnesium does not fall at all in the first time of magnesium deficiency [22,23].

Magnesium is a physiological calcium antagonist, so decreased extracellular magnesium leads to increase intracellular calcium [24]. Therefore, increasing extracellular levels of magnesium may have anti – inflammatory effect [25,26].

Thus, the mechanism of immune stress in magnesium deficiency may consist of a reduced extracellular magnesium / calcium antagonism as the result of decreased

plasma magnesium level.

Neuromediators play a major role in inflammation and in the production of OS. Nervous and immune systems interact bidirectionally. Magnesium deficiency leads to a stress response by releasing neurotransmitters such as substance P.

Another important pathway in magnesium deficiency – inflammation cascade is the activation of NFkB, which is a crucial factor in regulation of immune and inflammatory responses. NFkB is present in cytoplasm in an inactive form, and can be activated during the response to different stress conditions [27]. Low serum levels of magnesium induce activation of NFkB in cultured canine cerebral vascular smooth [20]. This supports an important role of the activation of NFkB in magnesium deficiency induced inflammation.

The inflammatory response is linked to oxidative damage during magnesium deficiency. There are several proofs indicating the presence of OS reactions in magnesium-deficient animals: enhanced tissue, lipoprotein peroxidation, reduced antioxidant status and increased plasma nitric oxide [28,29]. The macrophages and neutrophils generate superoxide anions, and are more responsive to activation by immune stimuli. This kind of activation is blocked by administration of a substance P receptor blocker, so the neurogenic inflammation linked to oxidative stress is present during magnesium deficiency [30].

### CONCLUSION

Almost all clinical entities associated with a low magnesium status are being characterized by a chronic inflammatory stress condition. Magnesium deficient state generate an inflammatory response: macrophage activation, release of inflammatory cytokines and production of free radicals.

The interplay of obesity, a chronic low-grade inflammatory condition, with magnesium deficiency vastly enhances the noxious influence of inflammation, promoting deleterious immune adaptations and ultimately increasing oxidative stress reactions.

The adverse role played by inflammation in the etiology of the most prevalent disease in modern society may support nutritional advice for the population to maintain a good bodyweight index and also an adequate intake of magnesium.

### References

1. Danaei G, Ding EL, Mozaffarian D, Taylor B et al. The preventable causes of death in the United States: comparative risk assesment of dietary, lifestyle, and metabolic risk factor. *PloS Med* 2009; 6(4):e1000058.
2. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. *J Clin Endocrinol Metab* 2008; 93:S9-S30.
3. Durlach J. Magnesium in Clinical Practice. John Libbey,

London 1988.

4. Rayssiguier Y, Mazur A, Durlach J. *Advances in Magnesium Research: Nutrition and Health*. John Libbey, London 2001, 502p.
5. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 1992; 267:1244-1252.
6. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006; 444:860-867.
7. Feinstein R, Kanety H, Papa MZ, Lunenfeld B, Karasik A. Tumor necrosis factor- $\alpha$  suppresses insulin-induced tyrosine phosphorylation of insulin receptor and its substrates. *J Biol Chem* 1993; 268:26055-26058.
8. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- $\alpha$ : direct role in obesity-linked insulin resistance. *Science* 1993; 259:87-91.
9. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissue of obese subjects release interleukin 6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab* 1998; 83:847-850.
10. Shimomura I, Funahashi T, Takahashi M, Maeda K et al. Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. *Nat Med* 1996; 2:800-803.
11. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; 112: 1796-1808.
12. Lumeng CN, DelProposto JB, Westcott DJ, Saltiel AR. Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. *Diabetes* 2008; 57: 3239-3246.
13. Gordon S. Alternative activation of macrophages. *Nat Rev Immunol* 2003; 3:23-35.
14. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; 372:425-432.
15. Fantuzzi G. Leptin: nourishment for the immune system. *Eur J Immunol* 2006; 36:3101-3104.
16. La Cava A, Matarese G. The weight of leptin in immunity. *Nat Rev Immunol* 2004; 4:371-379.
17. Hotamisligil GS, Erbay E. Nutrient sensing and inflammation in metabolic diseases. *Nat Rev Immunol* 2008; 8:923-934.
18. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have causal role in multiple forms of insulin resistance. *Nature* 2006; 440:944-948.
19. Weglicki WB, Phillips TM, Mak IT, Cassidy MM, Dickens BF, Stafford R, Kramer JH. Cytokines, neuropeptides, and reperfusion injury during magnesium deficiency. *Ann N Y Acad Sci*. 1994; 723:246-57.
20. Altura BM, Gebrewold A, Zhang A, Altura BT. Low extracellular magnesium ions induce lipid peroxidation and activation of nuclear factor- $\kappa$ B in canine cerebral vascular smooth muscle: possible relation to traumatic brain injury and strokes. *Neurosci Lett*. 2003;341(3):189-92.
21. Nielsen FH. Magnesium, inflammation, and obesity in chronic disease. *Nutr Rev*. 2010 Jun;68(6):333-40.
22. Malpuech-Brugère C, Nowacki W, Daveau M, Gueux E, Linard C, Rock E, Lebreton J, Mazur A, Rayssiguier Y. Inflammatory response following acute magnesium deficiency in the rat. *Biochim Biophys Acta*. 2000 ;1501(2-3):91-98.
23. Shogi T, Oono H, Nakagawa M, Miyamoto A, Ishiguro S, Nishio A. Effects of a low extracellular magnesium concentration and endotoxin on IL-1 $\beta$  and TNF- $\alpha$  release from, and mRNA levels in, isolated rat alveolar macrophages. *Magnes Res*. 2002 ;15(3-4):147-52.
24. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J*. 1984 ;108(1):188-93.
25. Bussière FI, Gueux E, Rock E, Girardeau JP, Tridon A, Mazur A, Rayssiguier Y. Increased phagocytosis and production of reactive oxygen species by neutrophils during magnesium deficiency in rats and inhibition by high magnesium concentration. *Br J Nutr*. 2002 ;87(2):107-13.
26. Bussière FI, Mazur A, Fauquert JL, Labbe A, Rayssiguier Y, Tridon A. High magnesium concentration in vitro decreases human leukocyte activation. *Magnes Res*. 2002;15(1-2):43-48.
27. Kabe Y, Ando K, Hirao S, Yoshida M, Handa H. Redox regulation of NF- $\kappa$ B activation: distinct redox regulation between the cytoplasm and the nucleus. *Antioxid Redox Signal*. 2005 ;7(3-4):395-403.
28. Petraut I, Zimowska W, Mathieu J, Bayle D, Rock E, Favier A, Rayssiguier Y, Mazur A. Changes in gene expression in rat thymocytes identified by cDNA array support the occurrence of oxidative stress in early magnesium deficiency. *Biochim Biophys Acta*. 2002;1586(1):92-98.
29. Rock E, Astier C, Lab C, Malpuech C, Nowacki W, Gueux E, Mazur A, Rayssiguier Y. Magnesium deficiency in rats induces a rise in plasma nitric oxide. *Magnes Res*. 1995;8(3):237-42.
30. Mak IT, Kramer JH, Weglicki WB. Suppression of neutrophil and endothelial activation by substance P receptor blockade in the Mg-deficient rat. *Magnes Res*. 2003;16(2):91-7.