

Physiology and Anatomy

Elixir Physio. & Anatomy 107 (2017) 47223-47227

Elixir
ISSN: 2229-712X

Platelet, Obesity and Metabolic Syndrome: A Fresh Look

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ARTICLE INFO

Article history:

Received: 2 May 2017;

Received in revised form:

9 June 2017;

Accepted: 20 June 2017;

Keywords

Metabolic syndrome,
Platelets,
Obesity,
Adipokines,
Chemokine.

ABSTRACT

Platelets play important physiological role in blood and participate primarily in thrombosis and hemostasis. However, they are highly activated in case of obesity and therefore contribute to the thrombosis and hemostasis. Obesity and MtS result into the thrombosis and hemostasis. Thus this work studies about how these adipokines and cytokines affect the platelets activity in obesity could help us in developing precise intervention to counter the obesity related vascular insufficiency.

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Introduction

Common Abbreviations Used:

TLR = Toll Like Receptor

TNFalpha = Tumor Necrosis Factor alpha

PF4 = Platelet Factor 4

IL = Interleukin

Insulin Resistance= InR

Metabolic syndrome: MtS

Platelets play important physiological role in blood and participate primarily in thrombosis and hemostasis. However, they are highly activated in case of obesity and therefore contribute to the thrombosis and hemostasis. Obesity and MtS result into the thrombosis and hemostasis. Obesity can cause the release of cytokines and adipokines that could directly activate the platelets. In this article we review the adipokine and non-adipokine dependent factors that could activate the platelets. We analyze both protective and deleterious adipokines as well as cytokines that could activate the platelets. These activated platelets can result into the thrombus formation and result into vascular insufficiencies such as ischemia and stroke. The knowledge of how these adipokines and cytokines affect the platelets activity in obesity could help us in developing precise intervention to counter the obesity related vascular insufficiency.

Background:

Platelets play crucial role in cellular events of thrombosis and hemostasis. These events were considered as their primary roles are still considered as important. Onset of obesity highly affects the platelets and produces a harmful effect ¹. Obesity can result into the overproduction of platelets and also increase in the number of circulating platelets that are activated ². These activated platelets are ready to adhere and aggregate, therefore increasing the possibility of thrombosis and atherosclerosis ³. It has already been demonstrated that increased calories, a common cause

for obesity, results into numerous endocrinological and immunological response ⁴. Platelets are crucial player in these responses, and therefore, directly participate in it. People affected by obesity are often characterized by Insulin Resistance (InR), Metabolic Syndrome (MtS) and cardio and cerebrovascular insufficiency. One quarter of US population is affected by MtS due to genetic and nutritional factors. Population that is genetically or nutritionally susceptible includes South Asians (Indian subcontinent), Southeast Asians (eg, Polynesian, Japanese), African-Americans, Hispanic, and Native Americans ⁵. Obesity results into the hyperplasia adipocytes and adjoining proliferative inflammatory tissue macrophages. Adipose tissues (White, Brown and recently discovered Beige Adipocytes) along with adipose tissue macrophage (ATMs), are much more than just a neutral energy depositing and dissipating tissues ^{6,7}. Instead, they are engaged into an elaborate endocrine activity releasing bioactive peptides, commonly termed as adipocytokines. Some adipocytokines are specifically released by adipocytes and are commonly termed as adipokines ⁸.

Platelets are terminally differentiated cells of myeloid origin produced by megakaryocytes of bone marrow. Platelets play important roles in thrombosis, hemostasis and are focus of intense study in vascular inflammation in diseases ⁹. The association of vascular insufficiency to the InR and MtS indicates that the platelets and endothelial cells play an active role in MtS. Upon onset of obesity, platelets can be recruited to the adipocytes and ATMs in response to the adipokines and therefore become the part of inflammatory setup that gives rise to the InR ⁷. While other component of vascular systems such as vascular smooth muscle cells (VSMCs) and pericytes are being investigated as a target cells in MtS, platelets and endothelial cells can directly participate into progression of MtS ¹⁰.

Platelets may play a dual role in MtS, one as an agent giving rise to the InR, the other as a cell that responds to the insulin and other chemokines.

Adipokines independent response:

Upon onset of obesity body elicits a response that is reminiscent of immunological response. Additional calories activate pathways that are both endocrinological as well as humoral in nature ^{11,12}. In this section we would discuss the common chemokines based response that can activate the platelets in case of obesity and MtS.

Chemokines, Obesity and Platelets:

Platelets, like macrophages, can directly communicate with the adipocytes and release the chemokines that can give rise to the InR. MtS including InR, obesity and diabetes are accompanied by low-grade inflammation as demonstrated by elevated level of PAI-1, IL-1, IL-6, IL-8, IL-12 and TNF alpha, RANTES (regulated on activation, normal T-cell expressed and secreted) ^{13 14,15}, MIP-1, MCP-1, C-reactive protein ¹⁶. Among these IL-1, IL-8 ¹⁷⁻¹⁹, RANTES ²⁰, PAI-1 ^{21,22} are also secreted by platelets and can therefore give rise to the InR. The other, however, can direct the platelet to an increased sensitivity towards the physiological agonists ². Onset of obesity results into increased circulation of activated platelets. Under pathological conditions, platelets can release mediators linking thrombosis and vascular inflammation such as the RANTES chemokine, PDGF, PF-4, Transforming Growth Factor- β (TGF- β), CD40 ligand (CD40L, CD154), P-selectin and Thromboxane A2 (TXA2) ^{23,24}. However, the adipocytes alone can trigger InR and therefore, platelet recruitment can only be a secondary response. As a consequence this could undermine the platelets role as a cause for the InR. In fact, the administration of TNFalpha alone in mice can stimulate the condition like InR ²⁵. While platelets respond to the TNFalpha, they do not secrete it themselves. Therefore, platelets mediated InR may not be a fruitful target of investigation in MtS.

However, it is apparent that the platelets respond to the inflammatory cytokines in obesity and MtS. Among these, IL-6 and TNF alpha are the most important. The activated platelet can further release inflammatory cytokines, such as Platelet Factor 4 (PF4) and RANTES, which can contribute to the InR, thus amplifying the inflammatory response ²⁶. Our and other's work ^{27,28} has demonstrated that PF4 activates the monocytes in a Kruppel Like Factor 4 (KLF4) dependent manner. This activation results in the differentiation of monocytes to macrophages, termed M4 macrophages for their unique surface markers ^{29,30}. These PF4 activated mono/mac have markers that are different than those seen in alternatively activated macrophages (AAMs). AAMs, on the other hand, are thought to enhance the insulin action and sensitivity in target tissues, thus playing a protective role ³¹. Therefore, release of PF4 can also contribute to development of InR.

TLRs:

Another aspect of the platelets' involvement in MtS involves Toll Like Receptors, TLRs ³². TLR4 is a pathogen sensing protein that responds to the lipopolysaccharides (LPS) of bacteria besides other pathogen surface molecules. TLR4 can also respond to the Free Fatty Acids (FFAs) in a same manner as it does to a LPS and FFAs ³³. TLR4 ablation results into the reduction of transformation of alternatively activated macrophages (M2, anti-inflammatory) into classically macrophages (M1, proinflammatory) which therefore can contribute to the InR ³⁴. Platelets have been

found to express TLR4 on their surface, and can therefore similarly respond to FFAs.

A further investigation is required to understand platelets specific TLRs' role in MtS.

Insulin and Platelets:

As a general rule, insulin plays a dampening role towards the platelets response to the agonists both *in vitro* and *in vivo* ³⁵. Therefore, the absence of insulin (as it happens in diabetes) can render the platelets hyperactive. Also, studies have suggested that supra-physiological levels of platelets, another common occurrence in diabetes, can activate the platelets ^{36,37}. In situations of insulin resistant diabetes, this can result into the pro-thrombotic state. Onset of InR and MtS also results into the reduction of insulin sensitivity associated molecules such as transcortin, transferrin, adiponectin, visfatin, omentin, ferritin and vaspin ³⁸. These molecules need individual attention for their role in platelet activation. Not only platelets but also their precursor cells, megakaryocytes, can be affected in obesity and MtS ²³. MtS effect on megakaryocytes can result into overproduction of platelets, synthesis of platelets that are refractory to the insulin's, abnormal platelets that have altered size and granularity of platelets. Megakaryocytes, themselves, can secrete chemokines that are the same or different than platelets. Platelet hyperactivity and hypercoagulability is deeply connected to the enhanced atherothrombotic risk of patients affected by obesity and MtS. The altered level of adipocytokines in MtS and InR can be an important determining factor for platelet abnormality.

Adipokines mediated response:

The mass-spectrometer and array based studies have discovered several adipokines in case of MtS that play protective and harmful role ³⁹. However, the most important that can contribute to the prothrombotic states and platelet activation is Leptin, Visfatin, Resistin and Endothelin ⁴⁰. Similarly, adipokines such as Apelin, Ghrelin and Adiponectin play protective role ⁴⁰. These adipokines have been studied for their roles in other target cells. However, their roles in platelet activation in obesity have not been fully studied. Studies have been performed using recombinant protein, transgenic mice and obesity model, to understand how the adipokines affect the platelet activity in case of obesity and MtS ⁴¹. A long term study to investigate the role of these adipokines in platelet activation *in vitro* and *in vivo* using obesity model can be critical for understanding this effect. In this section we would try to address the adipokines mediated role of platelet activation and obesity as well as MtS. We have individually addresses each of these adipokines and their possible effect on platelet activation or function, resulting into the pathogenesis of diseases. Structure, function and normal physiological role of each of these adipokines is beyond the scope of this article. However references have been included that would provide these information to the readers.

Leptin: Obesity results into the increased levels of leptin and the vascular action of leptin is considered as prothrombotic. Both platelets and megakaryocytes express a long form of leptin receptor (Ob-R) ⁴². The leptin potentiates platelet response to the physiological and synthetic agonists. These receptors therefore would make platelets more susceptible in case of obesity ⁴³. In recent studies it has been demonstrated that leptin's effect on platelets can be associated to the morbidity which can be reversed by the presence of adiponectin ⁴⁴. There is however conflicting data indicating

that leptin mediated signaling may not directly enhance the platelets sensitivity to the agonists²³.

Visfatin: Obesity and type 2 diabetes mellitus is accompanied by the increase in visfatin concentration in serum as indicated by some studies^{23,45}. Other studies have indicated the insulin like effect of visfatin in normal condition^{46,47}. Reports suggest that Visfatin can also make the platelets prothrombotic in nature⁴⁸. Although their binding to the insulin receptor on site different than insulin indicates their possible antithrombotic effect, the increased level in obesity calls for a closer investigation. Apparently, the level of visfatin in blood can be an important factor of its response and effect on platelets.

Resistin: Mice injected with resistin were found to develop the InR^{49,50}. Level of resistin is increased in the serum from obese mice. Resistin plays proinflammatory role via activation of NFkappaB. The prothrombotic effect of resistin has been explored in obesity. Resistin has been demonstrated to result into the release of P-Selectin from platelets, an important marker for their activation⁵¹.

Decorin: Isoforms of decorin has been described as a receptor for resistin in adipocyte progenitor cells. Decorin is secreted in case of obesity and supposed to have negative effect⁵². The expression of this receptor is still not fully tested in platelets and megakaryocytes although their interaction with it is reported⁵³. However some studies suggests its role on the ligand-binding activity in platelets promoting the platelets activity^{54,55}.

Endothelin: Increased level of endothelin is observed in case of obesity and MtS. Platelets are potential targets for endothelin-1 activity. There are conflicting reports suggesting both endothelin-1 based activation and inhibition in platelets⁵⁶. Platelets may express both endothelin A & B receptors. Few reports suggest that platelets activity is modulated by endothelins in case of obesity⁵⁷. Knock out for these receptors exist and used in mouse model for obesity. Perhaps the response of platelets to endothelin is similar to that of insulin and different doses of endothelin can have contrasting effect.

Adiponectin: Adiponectin plays protective role in MtS and is also considered anti thrombotic in nature⁵⁸. Adiponectin, however, has been associated with the antithrombotic activity on platelets⁵⁹. It clearly suppress the platelets activity even under the obese condition, making it a potential antagonist for the the obesity induced prothrombotic condition⁶⁰. Of course, adiponectin has added advantage of being vasculo-protective in nature⁶¹. Adiponectin has insulin-sensitizing effects and show anti-inflammatory effects in human. Platelets express AdipoR1 and AdipoR2, the isotypes of adiponectin receptors. AdipoR1 has been floxed and used for study in obesity model in previous studies⁶².

Apelin: Apelin and ghrelin^{40,63-66} have been suggested to play protective role as well as antithrombotic role in obesity. Apelin directly inhibits platelets activity and therefore could result into beneficial effects in obesity^{67,68}. Similarly the ghrelin also have positive effect on platelets activation and thrombosis^{66,69}.

Conclusion and Future Direction:

It is highly imperative to perform the studies to link platelet activation to the MtS and obesity as well as identifying the mechanistic basis for the phenomenon. An experimental approach to perform these studies could be to exploit conditional knockout mice using PF4-cre and Ob-R flox/flox mice that will generate platelet specific knockout

mice. This would explain the role of platelets in thrombosis during MtS.

The serum analytes from these mice could be subjected to ELISA to estimate the level of PF4 (as a marker of activation). Also, the intravital microscopy study could be performed (a thrombosis model) to explain platelets direct role in obesity induced ischemia. As an alternative approach the thrombopoietin knock out mice (TPOR^{-/-}) will be engaged in the studies. Since TPOR^{-/-} (a thrombopoietin receptor knockout mice) have reduced number of circulating platelets. These mice will be replenished with the platelets from wild type and Ob-R conditional knockout mice and the intravital microscopy study will be performed. Similarly, a chemokine array could be performed to get the obesity dependent chemokines from platelets.

The MtS is fast gripping the world on an epidemic proportion. Thrombosis and cardiovascular diseases are main outcomes of obesity and InR. Studying the effects of obesity on platelets will help in developing therapeutic targets that can reduce morbidity and mortality to a significant level. However, it does not undermines their importance in obesity induced platelet malfunction⁷⁰. In this article we have covered the common adipokines (Table 1). We have left the adipokines such as proinflammatory Lipocalin 2, RBP4, Lipocalin 2, ANGPTL2, TNF, IL6, IL18, CCL2, CXCL5, NAMPT and anti-inflammatory SFRP5. Also, we have used the atherosclerosis and thrombosis as an outcome of this effect. However, the role of obesity induced platelet malfunction in cancer cannot be ruled out. Cancer is highly correlated to the obesity and platelets are an important immunological cell that actually contributes to the progression of the cancer. Platelets do so by providing the growth factor as well as contributing to the immune-checkpoint. This effect is mediated by the activation of platelets which as we noticed is important outcome in obesity⁷¹. This, therefore, provides an additional reason to investigate “obesity-adipokine-platelet activation” axis as “the” most important pathogenic factor in obesity. Adipokines has potential for future pharmacological treatment strategies of obesity and its aftermath. The benefit of these therapies would directly be mediated via platelet activity. Identical to the macrophages, we assume that, platelets may have different, albeit, protective role when not activated. With this article we have attempted to explain the importance of platelets in obesity.

Table1.

Adipokine	Level in Obesity	Effect on Platelets
Leptin	Increased	Prothrombotic
Visfatin	Increased	Prothrombotic
Resistin	Increased	Prothrombotic
Decorin	Increased	Prothrombotic
Endothelin	Increased	Prothrombotic
Adiponectin	Decreased	Antithrombotic
Apelin	Increased	Antithrombotic
Ghrelin	Decreased	Antithrombotic

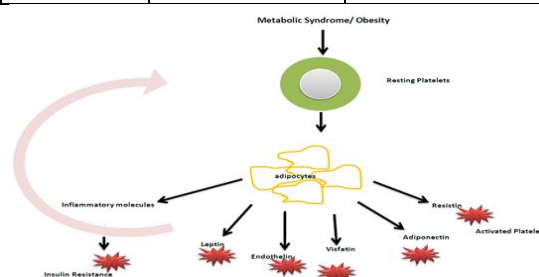


Figure 1. Activation of Platelet by MtS or obesity.

MtS /obesity put stress on resting platelet. Resting platelet binds to adipocytes and activates inflammatory molecules and different adipokines which results activation of platelet.

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