

## Case Report

## Open Access

Giovanni De Caridi, Mafalda Massara, Francesco Spinelli, Raffaele Grande, Lucia Butrico, Pierandrea Rende, Maurizio Amato, Rita Compagna, Bruno Amato, Stefano de Franciscis, Raffaele Serra \*

# An uncommon case of arterial aneurysms association with high plasma levels of Matrix Metalloproteinase-9 and Neutrophil Gelatinase-Associated Lipocalin

DOI: 10.1515/med-2015-0083

received October 24, 2015; accepted November 02, 2015.

**Abstract:** The association of an axillary artery aneurysm and an abdominal aortic aneurysm is extremely rare. In this study, we describe this association in a 69 year-old-man. We measured this patient's metalloproteinases (MMPs) and Neutrophil Gelatinase – Associated Lipocalin (NGAL) levels over a three years period before the abdominal aortic aneurysm rupture. We speculate that high serum levels of MMPs and NGAL may have a prognostic role and may predict aneurysm rupture in patients with an uncommon association of arterial aneurysms.

\***Corresponding author: Raffaele Serra:** Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro. Catanzaro, Italy; Interuniversity Center of Phlebology (CIFL). International Research and Educational Program in Clinical and Experimental Biotechnology. Headquarters: University Magna Graecia of Catanzaro, Catanzaro, Italy, E-mail: rserra@unicz.it  
**Giovanni De Caridi, Mafalda Massara, Francesco Spinelli:** Cardiovascular and Thoracic Department, University of Messina, Messina, Italy

**Raffaele Grande, Lucia Butrico, Stefano de Franciscis:** Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro. Catanzaro, Italy.

**Pierandrea Rende:** Department of Health Sciences, University Magna Graecia of Catanzaro. Catanzaro, Italy

**Rita Compagna, Bruno Amato:** Department of Clinical Medicine and Surgery, University Federico II of Naples. Naples, Italy; Interuniversity Center of Phlebology (CIFL). International Research and Educational Program in Clinical and Experimental Biotechnology. Headquarters: University Magna Graecia of Catanzaro, Catanzaro, Italy

**Stefano de Franciscis:** Interuniversity Center of Phlebology (CIFL). International Research and Educational Program in Clinical and Experimental Biotechnology. Headquarters: University Magna Graecia of Catanzaro, Catanzaro, Italy

**Stefano de Franciscis and Raffaele Serra** contributed equally to this work and share the senior authorship

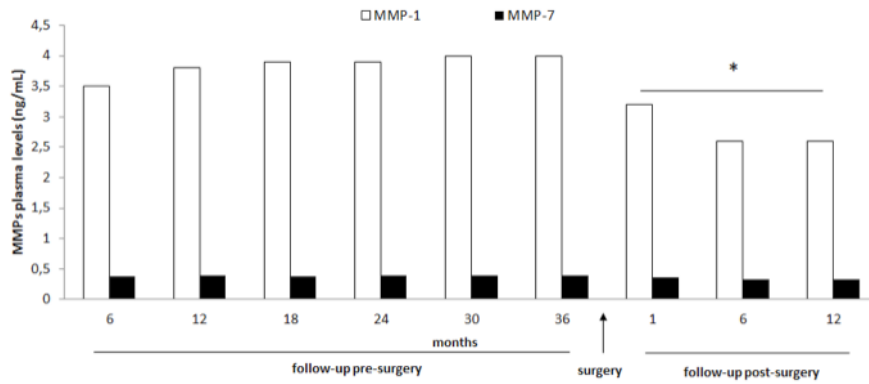
**Keywords:** Abdominal Aortic Aneurysm, Axillary Aneurysm, Matrix Metalloproteinase-9, Neutrophil Gelatinase – Associated Lipocalin

## 1 Introduction

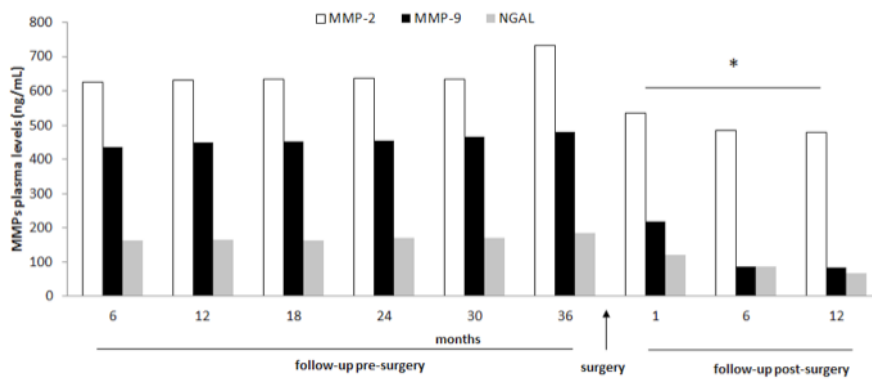
True aneurysms of the axillary artery are extremely uncommon [1-2] and even more uncommon when associated with abdominal aortic aneurysms. In fact, to the best of our knowledge no similar cases are reported in the current literature. Metalloproteinases (MMPs) are enzymes that regulate extracellular structural proteins and consequent tissue remodeling and seem to be involved in several vascular diseases [3]. Neutrophil gelatinase-associated lipocalin (NGAL) is a protein belonging to the lipocalin family and is expressed by activated neutrophils. It has the ability to positively modulate the activity of MMP-9 in particular by forming the NGAL/MMP-9 complex. This complex formation protects MMP-9 from proteolytic degradation [4]. We describe a 69-year-old-male with a concomitant sub-renal abdominal aortic aneurysm (AAA) and a large right axillary artery aneurysm who was admitted for surgical treatment of both the aneurysms in which high plasma levels of MMP-9 and NGAL were detected (Fig. 2).

## 2 Case Report

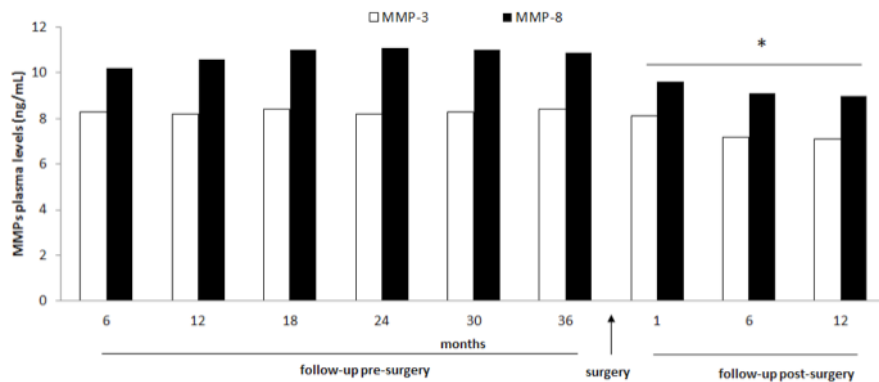
A 69 year-old-man with history of sub-renal abdominal aortic aneurysm (30 x 45 mm), hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD) and cardiomyopathy evaluated for the past three years in our operative unit through clinical and laboratory tests



**Figure 1:** Plasma levels of MMP-1 and MMP-7, measured through ELISA test in patients during the follow-up before and after the surgery. \*P<0.01 post-surgery vs pre-surgery.



**Figure 2:** Plasma levels of MMP-2, MMP-9 and NGAL, measured through ELISA test in patients during the follow-up before and after the surgery. \*P<0.01 post-surgery vs pre-surgery.



**Figure 3:** Plasma levels of MMP-3 and MMP-8, measured through ELISA test in patients during the follow-up before and after the surgery. \*P<0.01 post-surgery vs pre-surgery.

(MMPs and NGAL plasma evaluation; Fig 1-3) complained of an acute abdominal pain (Visual Analogical Scale score - VAS: 8). Computed tomography (CT) scan with contrast revealed the presence of a ruptured infrarenal abdominal aortic aneurysm (63 x 70 mm) and a right axillary artery

(43 x 60 mm) aneurysm with intraluminal thrombus. Clinical evaluation revealed the presence of a solid, palpable pulsating mass in the right axillary fossa. Motility and sensibility of the right hand was normal and the radial pulse was present. Ultrasound examination of

the upper limbs showed a right axillary artery aneurysm (40 x 60 mm). Brachial, radial and ulnar arteries were normal and patent. Ultrasound examination of the lower limbs showed normal and patent arteries. No sign of vasculitis or connective tissue disease (e.g. hyperelastic skin, hypermobile joints, or marfanoid habitus) was present. Laboratory tests including erythrocyte sedimentation rate, C reactive protein, complete blood count, serological test for syphilis, rheumatoid factor, antinuclear antibody, antithrombin III, protein C, and protein S were normal. In contrast, higher plasma levels of MMP-9 and NGAL were detected (Fig. 2). The axillary artery aneurysm was considered unsuitable for endovascular intervention due to tortuosity of the artery. A contemporaneous surgical treatment of both aneurysms was proposed in order to avoid repeated general anesthesia in a patient affected by chronic obstructive pulmonary disease.

Surgical repair of the aortic aneurysm (Fig. 4) was performed using an aorta-aortic bypass with Dacron 18 mm (Vascutek Ltd., Renfrewshire, Scotland, UK) through a median laparotomy and a sample of aneurysmal tissues was taken.

Then, open repair of the right axillary artery aneurysm (Fig. 5) was performed by ligation of the aneurysm followed by a bypass with an 8-mm Propaten polytetrafluoroethylene (PTFE) graft (WL Gore & Associates, Newark, Delaware).

Immunoblotting test performed on aneurysmal tissues from the axillary and abdominal aortic arteries taken at the time of the surgery (described in our previous study [5]) showed increased activation of both MMP-9 and NGAL in the aortic aneurysm tissue and of all MMPs and NGAL in the axillary artery aneurysm tissue with respect to normal tissue (healthy segments of aneurysmatic vessel) (Figs 6,7). The post-surgical period was uneventful: neurological examination of the right upper arm was normal and radial pulse was present. Seven days post-surgery, the patient was discharged on antiplatelet therapy (aspirin 100 mg/day). During follow-up visits at 1, 3, 6, 9 and 12 months, the prosthetic bypass of the right upper arm was patent and no post-surgical complications were seen. Moreover, during this time a significant decrease in plasma levels of MMPs and NGAL was recorded (Figs 1-3).

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.

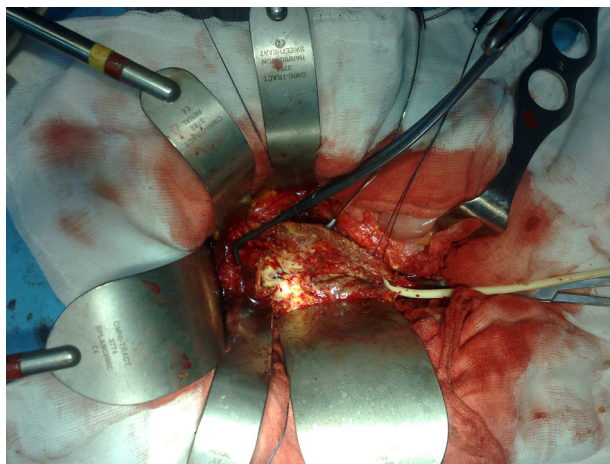


Figure 4: Aortic aneurysm.

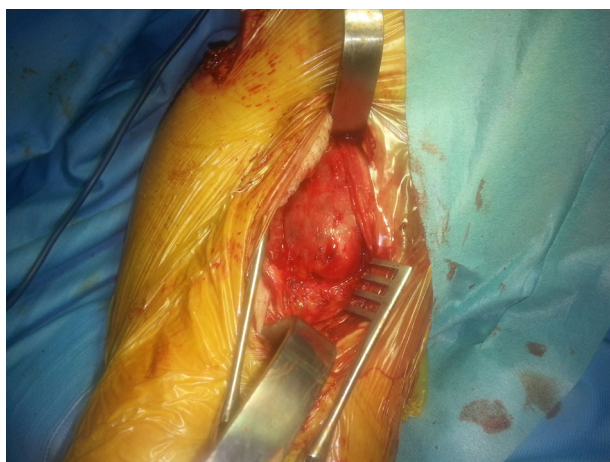
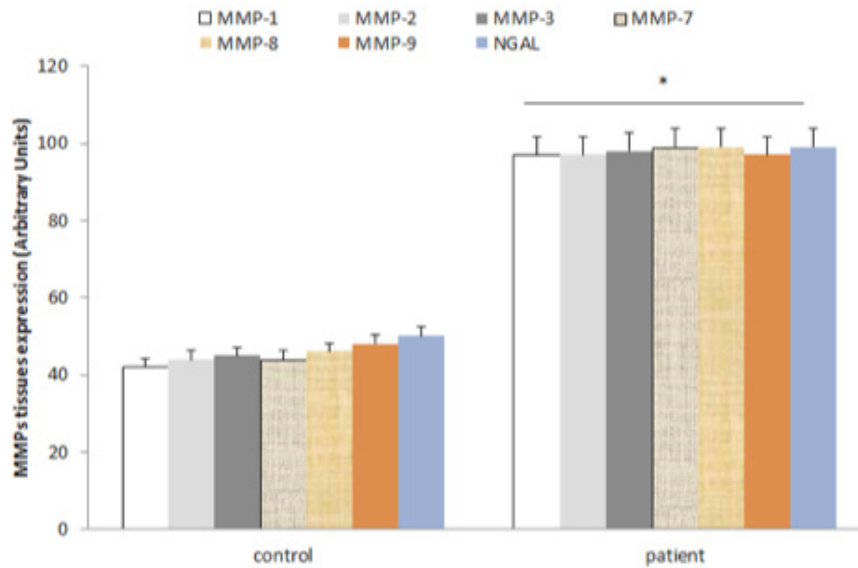


Figure 5: Right axillary artery aneurysm.

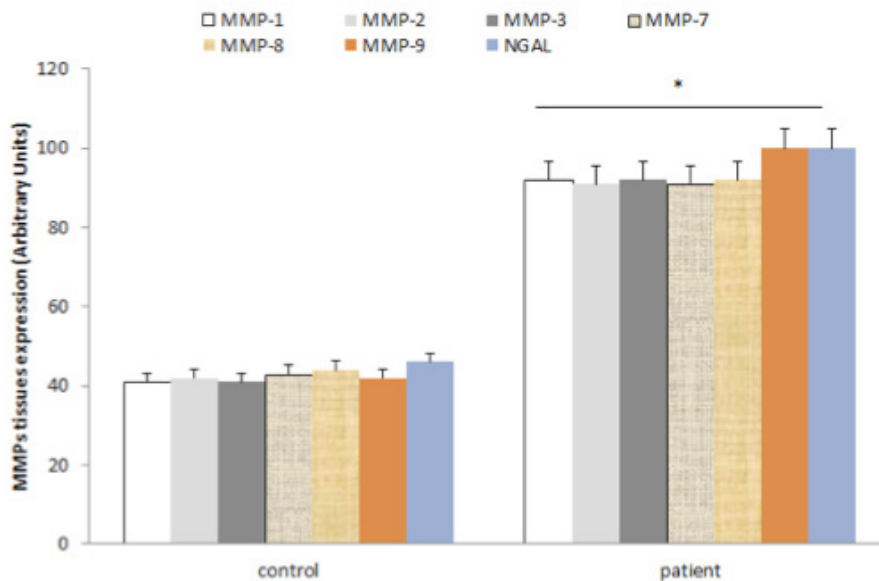
### 3 Discussion

Here, we report a patient admitted to our hospital for surgery of sub-renal AAA and right axillary artery aneurysm. Some authors have previously documented the presence of axillary artery aneurysm [6-11], very few papers have documented an association of abdominal and peripheral aneurysms [12-13]. Tanaka et al., [15] described a patient with multiple atherosclerotic aneurysms of the bilateral subclavian artery, aortic arch and abdominal aorta. Commonly, patients affected by abdominal aortic aneurysms present an aneurysm at the level of the femoral-popliteal segment [13-14].

Using Medline, PubMed, Embase, Cochrane library and Reference lists for articles published up to June 30 2014, we did not find any publications describing a contemporaneous presence of axillary artery aneurysms and with an infrarenal abdominal aortic aneurysm.



**Figure 6:** MMP-s and NGAL tissue expression in healthy and in aneurysmatic segments of the patient, measured through western blot analysis on the tissues taken from axillary artery aneurysm at the time of the surgery. \* $P < 0.01$ .



**Figure 7:** MMP-s and NGAL tissue expression in healthy and in aneurysmatic segments of the patient measured through western blot analysis on the tissues taken from abdominal aortic artery aneurysm at the time of the surgery. \* $P < 0.01$ .

Both early diagnosis and appropriate treatment are mandatory, in order to avoid major complications, e.g. thrombosis, distal embolization with acute ischemia of the hand and limb loss, compression of adjacent structures and rupture with blood loss that represents a life-threatening event.

Surgery is the gold standard of treatment, while endovascular management is an interesting, less invasive and attractive alternative, but long term results are still

unknown [15-16]. A contemporaneous surgical treatment of both aneurysms is feasible, without an increase in local and general complications.

As previously described, MMPs and NGAL play a pivotal role in the pathophysiology of both vascular [17-30] and non-vascular diseases [3]. According to the protocols reported in agreement with literature data [3,14-15] we detected in our patient during follow-up a time-dependent increase of MMP-1, -2, -3, -7, -8, and 9 plasma



levels. Moreover, at the time of the aneurysm rupture, higher levels of MMP-9 and NGAL were detected. Several authors have reported that zymography may also be used to identify both pro-MMPs and MMPs. In our present study, we used Western blot analysis with anti-MMPs able to identify the activated form of MMP; this could represent a limit of this study. However, as reported by Hu and Beeton [31] detection limits for Western Blots are often much lower than those of zymographic gels, potentially leading to false-negative results related to this technique.

In conclusion, in this uncommon case report we confirm the prognostic role of MMPs in the follow-up of patient with aneurysmal artery. Moreover, we can underline the role of MMP-9/NGAL complex during the rupture event.

The Authors received no funding.

The Authors declare no conflict of interest.

## References

- [1] Troutman DA, Mohan CR, Samhuri FA, Sohn RL. Open repair and endovascular covered stent placement in the management of bilateral axillary artery aneurysms. *Vasc Endovascular Surg.* 2010;44(8):708-9.
- [2] Gray RJ, Stone WM, Fowl RJ, Cherry KJ, Bower TC. Management of true aneurysms distal to the axillary artery. *J Vasc Surg.* 1998;28(4):606-10.
- [3] Malemud CJ. Matrix metalloproteinases (MMPs) in health and disease: an overview. *Front Biosci.* 2006;11:1696-701.
- [4] Singer E, Markó L, Paragas N, Barasch J, Dragan D, Müller DN, Budde K, Schmidt-Ott KM. Neutrophil gelatinase-associated lipocalin: pathophysiology and clinical applications. *Acta Physiol (Oxf).* 2013;207(4):663-72.
- [5] Serra R, Grande R, Montemurro E, Lucia Butrico, Caliò FG, Mastrangelo D, Scarcello E, Gallelli L, Buffone G, de Franciscis S. The role of Matrix Metalloproteinases and Neutrophil Gelatinase-associated Lipocalin in central and peripheral arterial aneurysms. *Surgery.* 2015;157(1):155-62.
- [6] Gray R, Stone W, Fowl R, Cherry K, Bower T: Management of true aneurysms distal to the axillary artery. *J Vasc Surg* 1998, 28:606–610.
- [7] Jhirad R, Kalman PG: Mycotic axillary artery aneurysm. *J Vasc Surg* 1998, 28:708-709.
- [8] Neumayer LA, Bull DA, Hunter GC, McIntyre KE, Yoshino MT, Aguirre ML, Bernhard VM: Atherosclerotic aneurysms of the axillary artery. A report of two cases and a review of the literature. *J Cardiovasc Surg (Torino)* 1992, 33:172–177.
- [9] Tripp HF, Cook JW: Axillary artery aneurysms. *Mil Med* 1998, 163:653–655.
- [10] Malik MK, Kraev AI, Hsu EK, Clement MH, Landis GS. Spontaneous axillary artery aneurysm: a case report and review of the literature. *Vascular* 2012, 20:46-48.
- [11] Michalakakis D, Lerais JM, Goffette P, Royer V, Brenot R, Kastler B. True isolated atherosclerotic aneurysm of the axillary artery. *J Radiol* 2003;84:1016-9.
- [12] Tanaka K, Makuuchi H, Naruse Y, Kobayashi T, Goto M, Arimura Y, Katsu M. Multiple atherosclerotic aneurysms of the bilateral subclavian artery, aortic arch and abdominal aorta. *Ann Thorac Cardiovasc Surg.* 2004;10(2):126-9.
- [13] Maksić M, Davidović L, Tomić I. Appearance of femoropopliteal segment aneurysms in patients with abdominal aortic aneurysm. *Vojnosanit Pregl.* 2012;69(9):783-6.
- [14] de Franciscis S, Mastroberto P, Gallelli L, Buffone G, Montemurro R, Serra R. Increased plasma levels of metalloproteinase-9 and neutrophil gelatinase-associated lipocalin in a rare case of multiple artery aneurysm. *Ann Vasc Surg.* 2013;27(8):1185.e5-7.
- [15] Niccoli Asabella A, Di Palo A, Rubini D, Zeppa P, Notaristefano A, Rubini G. [Distribution of 18F-FDG in a patient with evolving abdominal aortic aneurysm]. *Recenti Prog Med.* 2012;103(11):552-4.
- [16] He C, Wu X, Cao J, Fan X, Liu K, Liu B. Endovascular management of spontaneous axillary artery aneurysm: a case report and review of the literature. *J Med Case Rep.* 2013;7(1):140.
- [17] Troutman DA, Mohan CR, Samhuri FA, Sohn RL. Open repair and endovascular covered stent placement in the management of bilateral axillary artery aneurysms. *Vasc Endovascular Surg.* 2010;44(8):708-9.
- [18] Serra R, Buffone G, Costanzo G, Montemurro R, Scarcello E, Stillitano DM, Damiano R, de Franciscis S. Altered Metalloproteinase-9 expression as the least common denominator between Varicocele, Inguinal Hernia and Chronic Venous Disorders. *Ann Vasc Surg.* 2014;28(3):705-9.
- [19] Amato B, Coretti G, Compagna R, Amato M, Buffone G, Gigliotti D, Grande R, Serra R, de Franciscis S. Role of matrix metalloproteinases in non-healing venous ulcers. *Int Wound J.*
- [20] Serra R, Buffone G, Falcone D, Molinari V, Scaramuzzino M, Gallelli L, de Franciscis S. Chronic venous leg ulcers are associated with high levels of metalloproteinases-9 and neutrophil gelatinase-associated lipocalin. *Wound Repair Regen.* 2013;21(3):395-401.
- [21] Serra R, Grande R, Butrico L, Buffone G, Caliò FG, Squillace A, Rizzo BA, Massara M, Spinelli F, Ferrarese AG, De Caridi G, Gallelli L, de Franciscis S. Effects of a new nutraceutical substance on clinical and molecular parameters in patients with chronic venous ulceration. *Int Wound J.* 2014, Feb. 25.
- [22] Serra R, Gallelli L, Buffone G, Molinari V, Stillitano DM, Palmieri C, de Franciscis S. Doxycycline speeds up healing of chronic venous ulcers. *Int Wound J.* 2015;12(2):179-84.
- [23] Serra R, Gallelli L, Conti A, De Caridi G, Massara M, Spinelli F, Buffone G, Caliò FG, Amato B, Ceglia S, Spaziano G, Scaramuzzino L, Ferrarese AG, Grande R, de Franciscis S. The effects of Sulodexide on both clinical and molecular parameters in patients with mixed arterial and ulcers of lower limbs. *Drug Des Devel Ther.* 2014;8:519-27.
- [24] Serra R, Grande R, Buffone G, Molinari V, Perri P, Perri A, Amato B, Colosimo M, de Franciscis S. Extracellular matrix assessment of infected chronic venous leg ulcers: role of metalloproteinases and inflammatory cytokines. *Int Wound J.* 2014. doi: 10.1111/iwj.12225.

- [25] Busceti MT, Grande R, Amato B, Gasbarro V, Buffone G, Amato M, Gallelli L, Serra R, de Franciscis S. Pulmonary Embolism, Metalloproteinases And Neutrophil Gelatinase Associated Lipocalin. *Acta Phlebol.* 2013;14:115-21.
- [26] Serra R, Grande R, Buffone G, Scarcello E, Tripodi F, Rende P, Gallelli L, de Franciscis S. Effects of glucocorticoids and TNF- $\alpha$  inhibitors on both clinical and molecular parameters in patients with Takayasu Arteritis. *J Pharmacol Pharmacother.* 2014;5(3):13-6.
- [27] Serra R, Grande R, Gallelli L, Rende P, Scarcello E, Buffone G, Caliò, FG, Gasbarro V, de Franciscis S. Carotid body paragangliomas and Matrix Metalloproteinases. *Ann Vasc Surg.* 2014;28(7):1665-70.
- [28] Serra R, Volpentesta G, Gallelli L, Grande R, Buffone G, Lavano A, de Franciscis S. Metalloproteinases-9 and Neutrophil Gelatinase-Associated Lipocalin Plasma and Tissue Levels Evaluation in Middle Cerebral Artery Aneurysms. *Br J Neurosurg.* 2014, May 5.
- [29] Amato B, Compagna R, Della Corte GA, Martino G, Bianco T, Coretti G, Rossi R, Braucci A, Aprea G, Zeppa P, Puzziello A, Terranova C. Peripheral blood mono-nuclear cells implantation in patients with peripheral arterial disease: a pilot study for clinical and biochemical outcome of neoangiogenesis. *BMC Surg.* 2012;12 Suppl 1:S1.
- [30] de Franciscis S, Grande R, Butrico L, Buffone G, Gallelli L, Scarcello E, Caliò FG, Fugetto F, Gasbarro V, Amato B, Serra R. Resection of carotid body tumors reduces arterial blood pressure. An underestimated neuroendocrine syndrome. *Int J Surg.* 2014;12 Suppl 1:S63-7.
- [31] Hu X., Beeton C. Detection of Functional Matrix Metalloproteinases by Zymography. *J Vis Exp.* 2010; 45:2445.