

# Anterior ischemic optic neuropathy associated with metabolic syndrome

*Neuropatia óptica isquêmica anterior associada a síndrome metabólica*

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## ABSTRACT

**Purpose:** Metabolic syndrome denotes a common cluster of naturally connected risk factors including obesity, elevated blood pressure, insulin resistance, dyslipidemia, proinflammatory state and prothrombotic state. Anterior ischemic optic neuropathy is an acute ischaemic disorder of the optic nerve head and may lead to severe visual loss. **Methods:** We considered three patients with moderate degree of diabetic retinopathy and anterior ischemic optic neuropathy. They were submitted to endocrinological examination and the diagnosis of metabolic syndrome was established. **Results:** Cardiological examination revealed that blood pressure control was not optimal. The signs of left ventricular hypertrophy and diastolic dysfunction were confirmed by echocardiography. They are possible markers of preclinical cardiovascular disease. **Conclusion:** We observed that a variety of well-known risk factors in metabolic syndrome may be involved in serious eye and cardiological complications. The early diagnosis and treatment of these patients can not only improve visual function but also prevent cardiovascular complications.

**Keywords:** Metabolic syndrome X; Optic neuropathy, ischemic; Cardiovascular diseases

## INTRODUCTION

Anterior ischemic optic neuropathy (AION) represents an acute ischemic disorder of the optic nerve and may lead to severe visual loss. Clinically it is classified into two groups: arteritic (A-AION) caused by giant cell arteritis and non-arteritic (NA-AION)<sup>(1)</sup>. The pathogenesis of NA-AION is not completely understood. NA-AION is a multifactorial disease. In addition to predisposing anatomic factors, systemic factors play an important role in the pathogenesis of NA-AION<sup>(1-2)</sup>. Systemic risk factors (arterial hypertension, diabetes mellitus, obesity, dyslipidemia etc.) are proved to have an influence on microcirculation and blood flow autoregulation of the optic nerve head<sup>(1,3)</sup>. We consider the connection between metabolic syndrome and NA-AION.

The definition of metabolic syndrome (MS) has been given by the WHO, the American Association of Clinical Endocrinologists (AACE) and the Adult Treatment Panel III report of the National Cholesterol Education Program (ATP III)<sup>(4-5)</sup>. They identify six components of the MS related to cardiovascular disease (CVD): abdominal obesity, atherogenic dyslipidemia, arterial hypertension (HTA), insulin resistance and/or glucose intolerance, pro-inflammatory state and prothrombotic state. Further diagnostic criteria have been postulated by the International Diabetes Federation (IDF)<sup>(6)</sup>.

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Current concepts of treatment of MS and vascular complications are medically supervised lifestyle changes, treatment of obesity with diet, increased physical activity and medical treatment for diabetes and hypertension<sup>(4-5)</sup>.

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## METHODS

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We considered three patients with MS and NA-AION. Diagnosis of MS was established by an endocrinologist according to the latest diagnostic criteria (ATP III and IDF). A person has MS if three of the following five conditions are observed:

- body mass index (BMI) >30 kg/m<sup>2</sup> and waist circumference ≥102cm in men and ≥88cm in women.
- Elevated fasting glucose level ≥110mg/dl (≥6.1 mmol/l), elevated hemoglobin A1c (HbA1c) >6.8% or if the person has been receiving drug treatment for elevated glucose level.
- High-density lipoprotein cholesterol (HDL) level <40 mg/dl (<1.04 mmol/l) in men and <50 mg/dl (<1.30 mmol/l) in women or if the person has been receiving drug treatment for reduced HDL level.
- Triglyceride level >150 mg/dl (>1.70 mmol/l) or if the person has been receiving treatment for elevated level of triglyceride.
- Hypertension (HTA) was determined as blood pressure ≥140/90 mmHg or if the person has been receiving treatment for hypertension.
- Proinflammatory state was determined by elevated levels of C-reactive protein and fibrinogen.

Standard ophthalmological examination and fluorescein angiography were performed. Cardiological examination included: evaluation of objective state, blood pressure control, electrocardiography (ECG), echocardiography and color Doppler of the carotid arteries. Other diseases were noted as well.

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## CASE PRESENTATION

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### Case 1

A 43-year-old male was hospitalized at the Medical Retina Department in March 2006 because of deterioration of vision in his left eye. Previous history revealed a deterioration of vision in the right eye five months before, when he was examined by an ophthalmologist and endocrinologist. He was diagnosed with type 2 diabetes mellitus *de novo*, arterial hypertension, type IIb hyperlipoproteinemia and a state following an insult of the occipital part of right hemisphere.

Ophthalmic examination revealed that his right eye visual acuity (VA) was 0.2 and his left eye VA was 0.7. Intraocular pressure was normal. Relative afferent pupillary defect was observed in the right eye. Pupillary reaction was normal in the left eye. The fundus features of both eyes and fluorescein angiography of the left eye are shown in figure 1.

Endocrinological evaluation demonstrated obesity and body mass index (BMI) of 36.2 kg/m<sup>2</sup>. Serum analyses showed elevated glucose and HbA1c (171 mg/dl; 11.5% respectively). Serum lipid levels including cholesterol, LDL and triglycerides were within normal values but HDL was reduced (36 mg/dl). Inflammatory markers were positive. C-reactive protein was 11.2 mg/l. Microalbuminuria was also observed: 64.5 mg/l.

A cardiological examination revealed that patient had no symptoms of cardiac ischemic disease. Values for arterial blood pressure in ambulatory conditions and at home were equivalent to first degree hypertension with a dominant raise observed in diastolic pressure (140/100 mmHg). The results of objective examination and electrocardiogram were normal. Echocardiogram showed an enlargement of the left atrium (5 cm), an initial stage of left ventricular hypertrophy (LV mass 282.2 g, LV mass/BSA 125 g/m<sup>2</sup>) and signs of diastolic dysfunction of left ventricle (E/A 0.8/1.27 m/s). A color Doppler scan of carotid arteries showed fibrous plaque on bifurcation of the left carotid artery with 20% maximum stenosis. The patient followed the recommended endocrinological therapy for six months and his serum analysis improved significantly: glucose, HbA1c and serum lipids were normal. He was on corticosteroid treatment for 3 weeks. His VA improved: right eye 0.5 and left 1.0 with correction. Fundus clinical features improved as well.

### Case 2

A 50-year-old female was examined at the Medical Retina Department in November 2005 because of deterioration of vision of her left eye. Five years before she had been diagnosed with type 2 diabetes, dyslipidemia and was receiving treatment for hypertension. An ophthalmic examination revealed that her right eye VA was 1.0 and her left eye VA gradually decreased in two weeks from 0.9 to 0.05. Intraocular pressure was normal in both eyes.

She was referred to an endocrinologist for further investigation and treatment. BMI was 26.5 kg/m<sup>2</sup> and waist circumference 95 cm. Serum analyses revealed elevated glucose and HbA1c (122 mg/dl and 8.5% respectively). Serum lipids were increased: cholesterol (410 mg/dl) and triglycerides (870 mg/dl). Proinflammatory markers were negative. A cardiological examination showed no symptoms of myocardial ischemia. The values for arterial blood pressure were equivalent to HTA of second degree (160/100 mmHg). Results of objective examination were normal. An ECG showed sinus rhythm with an incomplete block of right bundle branch. Echocardiography showed enlargement of the left atrium (4.6 cm) and signs of diastolic dysfunction of the left ventricle (E/A 0.6/1.0 m/s). A color Doppler scan of carotid arteries showed calcified plaque on bifurcation of right carotid artery with 25% maximal stenosis. The patient was on low doses of corticosteroids for two months. She followed her diet regimen strictly and took regularly medications for diabetes and

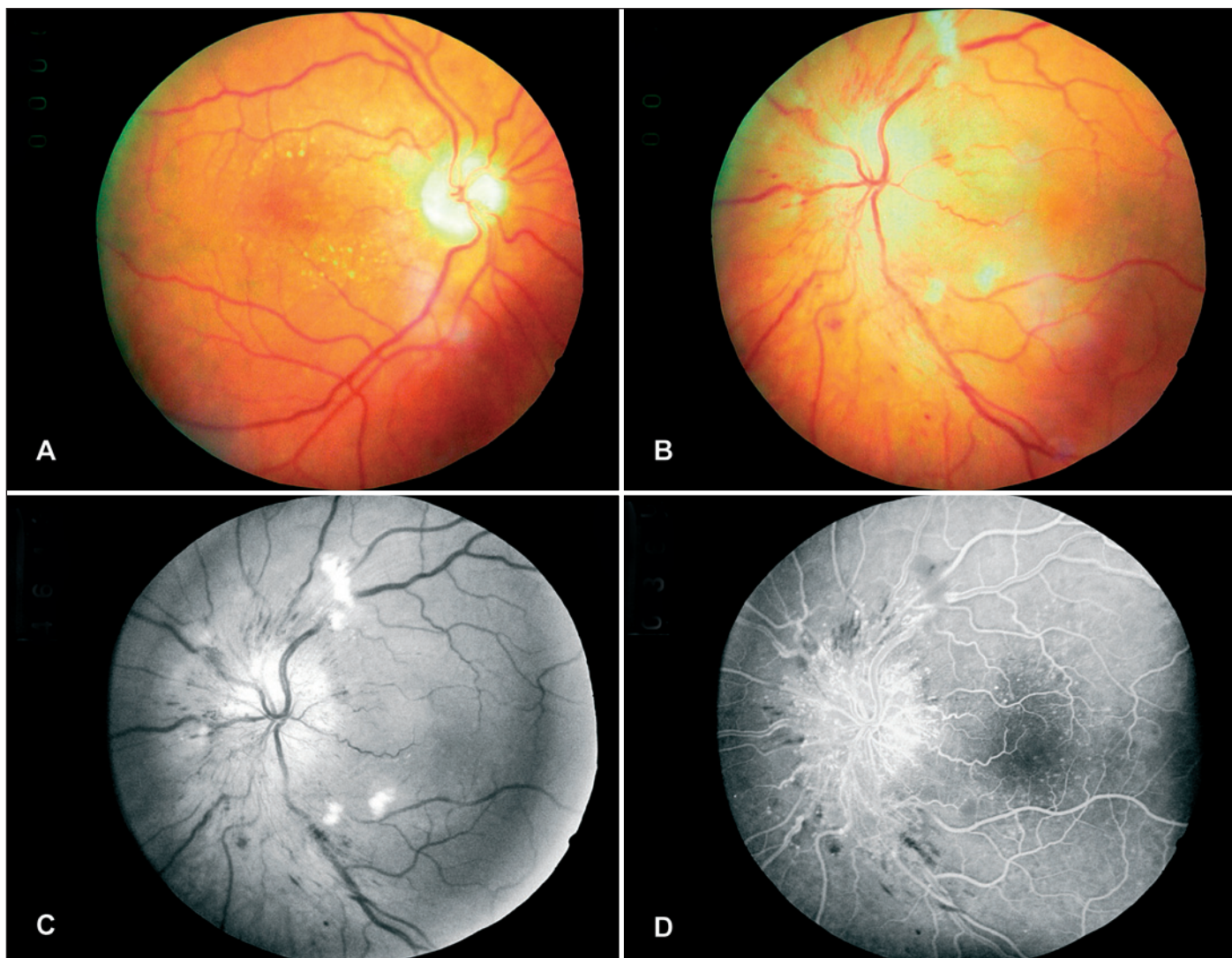


Figure 1 - Fundus photographs of both eyes and red-free as well as fluorescein angiogram of the left eye. A) Fundus of right eye. Optic disc is pale and flat (optic disc atrophy after AION) with changes in retinal vessels and moderate diabetic retinopathy; B) Fundus of left eye. Swollen ischemic optic disc (acute AION), cotton wool exudates, moderate-severe diabetic retinopathy; C) Red free of the left eye shows cotton wool spots and dot hemorrhages, optic nerve with undefined border; D) Fluorescein angiography of left eye, venous phase (36 sec): capillaries of the optic disc are dilated and leak profusely. Stasis of the retinal veins, peripapillary hemorrhages, many microaneurisms around the macula are also observed.

hypertension. Four months later her serum analysis improved: glucose and HbA1c were normal, total cholesterol was normal, HDL increased to 45 mg/dl, LDL was normal and triglycerides were increased (326 mg/dl). VA in her left eye improved to 0.7.

### Case 3

A 55-year-old female was examined at the Medical Retina Department in April 2006, because of deterioration of vision in her right eye. Her past medical history included obesity (BMI 32.4 kg/m<sup>2</sup>) and hypertension which had lasted more than 25 years (since pregnancy). She has been on treatment since then, but was not examined regularly by a cardiologist. In November 2005 she had a diagnosis of type 2 diabetes (*de novo*), type IIb hyperlipoproteinemia and polyradiculoneu-

ritis. Basic ophthalmological examination revealed that her right VA was 0.1 and left VA was 0.9-1.0. Intraocular pressure was normal in both eyes. The features of fundus and fluorescein angiography of the right eye are shown (Figures 3A and 3B).

A special investigation included endocrinological and cardiological examinations. Her BMI was 32.4 kg/m<sup>2</sup> and her waist circumference 97 cm. Serum analysis showed increased glucose and HbA1c (110 mg/dl and 8.0%). Proinflammatory markers were negative. High levels of serum cholesterol, LDL and triglycerides were observed (315 mg/dl, 231 mg/dl and 168 mg/dl). HDL was normal. Cardiological examination showed no symptoms of ischemic heart disease. There was arterial hypertension of third degree (190/120 mmHg). Results of her objective examination were

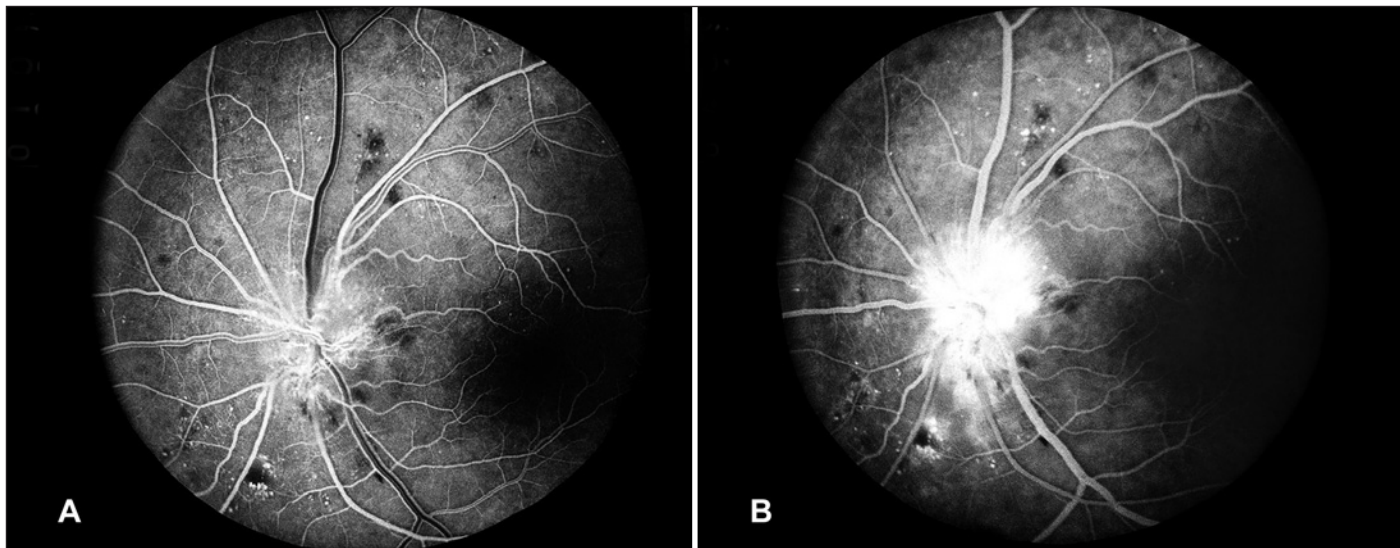


Figure 2 - Fluorescein angiography of the left eye. A) Early phase shows dilatation of prelaminar capillary network of the optic disc and some leakage of dye; B) Late phase shows profuse leakage of dye in the optic disc. Some microaneurysms and dot hemorrhages are also observed.

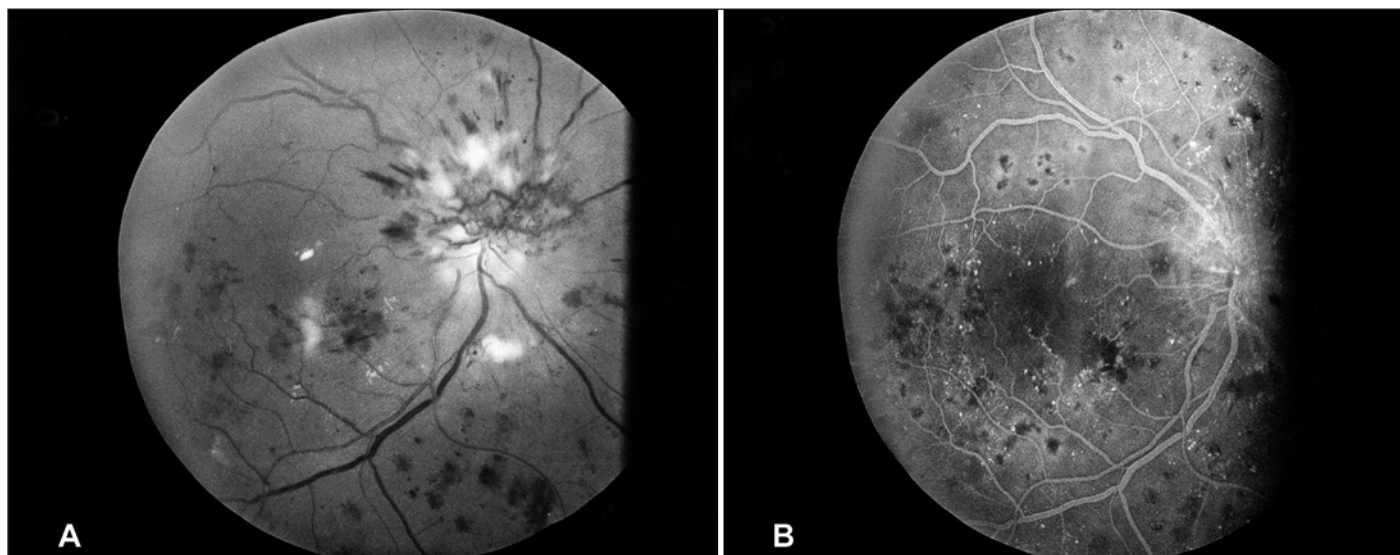


Figure 3 - Red-free and fluorescein angiogram of the right eye. A) Swollen venous ischemic optic disc, splinter-shaped peripapillary haemorrhages (acute AION). Ischemic diabetic maculopathy. Severe non-proliferative diabetic retinopathy was diagnosed; B) Fluorescein angiography shows dilatation of prelaminar capillary network, moderate macular capillary closure, one month after laser treatment.

normal. An ECG showed left ventricular hypertrophy. Echocardiography showed left atrium enlargement (4.9 cm), left ventricular hypertrophy (LV mass 342 g, LV mass/BSA 178 g/m<sup>2</sup>) and signs of diastolic dysfunction. The patient was on strict diet and took medications regularly. After only one month of treatment her serum analyses improved and were within normal limits, except for triglycerides which were still increased (203 mg/dl). Disc edema of the right eye resolved but moderate ischemic diabetic maculopathy remained. Because of pre-proliferative diabetic retinopathy she was submitted to laser photocoagulation treatment. Her best corrected VA improved to 0.7.

## DISCUSSION

It is confirmed that factors related to optic disc structure play a role in the pathophysiology of NA-AION<sup>(7)</sup>. Patients with MS have increased risk of developing NA-AION because of clustering and synergistic effect of systemic metabolic factors<sup>(3)</sup>. In our patients, we considered the influence of systemic factors related to MS in the pathogenesis of NA-AION. Common features of our three patients were that they were middle-aged (mean age 48.6). Their metabolic disorders were diagnosed late and numerous examinations revealed various complications. The visual disorder was the first serious problem that

alerted our patients to seek medical help and an ophthalmologist was the first physician to examine them.

In our first patient, retinal vascular complications include optic disc atrophy after AION in his right eye and acute AION in left eye within six months. After this second eye complication, he was submitted to a strict treatment for obesity, diabetes, HTA and HLP. VA in the right eye improved partially. Clinical features and VA in the left eye improved as well.

According to the literature, there is no effective and well-established therapy for NA-AION, either for visual recovery or for prophylaxis against involvement of the second eye<sup>(1)</sup>. The incidence of AION in the second eye is quite high, particularly in young diabetics (<45 years)<sup>(1)</sup>.

Our third patient had obesity and hypertension for more than 25 years, while diabetes and HLP were more recently diagnosed. She followed the prescribed therapeutic regimen and improved her metabolic control within six months. Clinical features and VA in the right eye improved partially.

We believe the clinical findings of this current series are a variety of papillophlebitis which should be treated immediately to try to avoid optic nerve atrophy and irreversible visual loss<sup>(8)</sup>.

Patients with MS have an increased risk of CVD<sup>(4-5)</sup>. In the current series of patients symptoms of coronary disease did not exist. However, structural and functional disturbances of the left ventricle-myocardial hypertrophy and diastolic dysfunction existed. In the third presented patient these disturbances were most significant and could be explained by long-term irregular control of arterial blood pressure. In all three patients HTA can be considered to be closely related to the development of the diagnosed myocardial hypertrophy and it is also an independent predictor of diastolic dysfunction<sup>(9)</sup>. Along with these factors the development of diastolic dysfunction includes increased BMI and DM<sup>(10)</sup>. Early recognition of diastolic dysfunction as well as proper treatment can prevent heart failure, coronary heart disease and death.

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### CONCLUSION

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We observed that a variety of well-known risk factors in MS may be involved in serious eye and cardiologic complications. In patients with NA-AION associated with MS a multidisciplinary approach is necessary in order to identify these risk factors. The early diagnosis and treatment of these patients can not only improve visual function but also prevent cardiovascular and cerebrovascular complications.

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### RESUMO

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**Objetivo:** A síndrome metabólica indica um grupo comum dos seguintes achados clínicos: obesidade, hipertensão arterial,

variações nos níveis de glicemia, dislipidemia, estado pró-inflamatório e o estado protrombótico. Neuropatia óptica isquêmica anterior é um distúrbio agudo isquêmico da cabeça do nervo óptico que pode levar à perda de visão. **Métodos:** Consideramos três pacientes com retinopatia diabética não proliferativa moderada e neuropatia óptica isquêmica anterior. Os pacientes foram examinados por endocrinologistas e o diagnóstico de síndrome metabólica foi confirmado. **Resultados:** O exame cardiológico revelou que o controle da pressão sanguínea não era adequado e tal anormalidade foi corrigida. A ecocardiografia confirmou os indícios de hipertrofia ventricular esquerda e disfunção diastólica. Estes são os marcadores possíveis da doença cardiovascular pré-clínica. **Conclusão:** Concluímos que os fatores de risco bem conhecidos, combinados na síndrome metabólica levaram às complicações oculares e às complicações cardiológicas. O diagnóstico antecipado e o tratamento destes pacientes pode não apenas melhorar a função visual mas também impedir as complicações cardiovasculares.

**Descritores:** Síndrome X metabólica; Neuropatia óptica isquêmica; Doenças cardiovasculares

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