Disappearance of acanthosis nigricans following discontinuation of niacin despite minimal change in insulin sensitivity

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Abstract A case report of a 40-year male patient who had elevated triglyceride (TG 2.98 mmol/l), and low HDL-C, 0.75 mmol/l which responded well to niacin. However, he developed acanthosis nigricans within three months of treatment. Insulin sensitivity index was studied while patient was on niacin and repeated 4.5 months after discontinuation of the drug.

Acanthosis nigricans cleared spontaneously, although the low insulin sensitivity (IS) persisted for 4.5 months after stopping niacin. This indicates that acanthosis nigricans was not related to the severity of duration of insulin resistance induced by niacin.

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Niacin is a B vitamin that when given in pharmacological doses, has profound lipid lowering effect. It stimulates the lipoprotein lipase activity and inhibits the VLDL synthesis and secretion from the liver which results in decreasing the level of plasma VLDL-C and HDL-C and increasing the plasma HDL-C. The commonest side effects are cutaneous flushing, nausea and abdominal cramps. Other side effects include glucose intolerance secondary to decreased insulin sensitivity, hyperuricemia and rarely acanthosis nigricans. However, in this patient, acanthosis nigricans persisted 4.5 months after stopping niacin.

Case report A 40-year old man was seen at the Lipid Clinic with triglyceride (TG) 2.98 (N < 1.98 mmol/l), and high density lipoprotein HDL-C 0.75 mmol/l (N > 1 mmol/l) detected in routine blood screening by the family physician. The patient was treated with gemfibralosol for a period of 6 weeks but this was discontinued because it caused decreased white cell count (leukopenia). He had hypertension, migraine headaches and chronic mild elevation of liver enzymes not related to gemfibralosol therapy.

His father died with acute MI at the age of 58 and his mother had hypertension and low HDL-C.

His weight was 71.8 kg, height 167 cm with BMI of 25.75. Blood pressure was 120/80. The physical examination was completely normal with no stigmata of hyperlipidemia.

Laboratory investigation revealed that cholesterol was 5.03 mmol/l, triglycerides 2.98 mmol/l, LDL-C 2.94 mmol/l, HDL-C 0.75 mmol/l, apoA-I 93 mg/dl (N 110-150 mg/dl), apoB 33 mg/dl (N 40-120 mg/dl), glucose 5.2 mmol/l, creatinine 89, uric acid 312, AST 38 uM/l, ALT 58, HBsAg was negative CBC, platelet, thyroid functions tests were normal. Diet and exercise regimes were prescribed but there was no response to these measures. Niacin was added in incremental doses of up to 1500 mg/day plus small doses of aspirin (1/2 tablet) before the niacin dose. He tolerated the drug very well and within 3 months his TG level decreased to 1.4 mmol/l, HDL-C increased to 0.90 mmol/l. However, he noticed darkness of his skin in the neck, axilla, cubital fossa and abdominal wall, mainly around the umbilical area. A diagnosis of acanthosis nigricans was made. He had urinary frequency, nocturia but no polydipsia.

Oral glucose tolerance test (OGTT) was done and insulin sensitivity was measured by frequent sampling intravenous glucose tolerance test.

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Insulin sensitivity was measured by FSIVGTT - modified minimal model\textsuperscript{9,10,11} glucose 0.3 gm/kg was injected at 0 time and tolbutamid 300mg at 20 minutes. Frequent blood samples for insulin and glucose were taken at -20, -15, -10, -5.
0, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 23, 24, 25, 26, 27, 28, 29, 31, 35, 40, 50, 60, 70, 80, 100, 120, 140, 160, 180, first while the patient was on niacin 1500mg/d and having acanthosis nigricans specifically 6 months from starting niacin treatment (Figs. 1, 2) and also repeated 4.5 months after discontinuation of niacin, 1.5 months after total disappearance of acanthosis nigricans (Figs. 3, 4). Insulin sensitivity index (SI) was 1.3 E-04 while patient on niacin and 1.6 E-04 after stopping niacin.

**Fig. 3** - Insulin level during FSIVGTT, 4 months after discontinuation of niacin and 1.5 months after total disappearance of acanthosis nigricans.

**Fig. 4** - Glucose level during FSIVGTT, 4 months after discontinuation of niacin and 1.5 months after total disappearance of acanthosis nigricans.
Discussion Acanthosis nigricans is a dark brown pigmented papillomatous-keratotic skin lesion. It is usually classified as malignant or benign forms. The malignant form of acanthosis nigricans usually exists with internal malignancy; an adenocarcinoma is found in the stomach in about 60% of patients, elsewhere in the abdominal region in 30%, and extra abdominally in about 10%.12,13

Benign acanthosis nigricans can be associated with hereditary syndromes like Prader-willii, Berardinelli-seip or with simple obesity which usually regresses with weight loss. Endocrine diseases including acromegaly, Cushing's syndrome and polycystic ovary and certain drugs like niacin.9 Oral contraceptives14 and steroids15 can be associated with benign acanthosis nigricans.

Acanthosis nigricans is histologically identical in the presence or absence of internal malignancy, endocrinopathy and obesity. Microscopically, the plaques have a wavy surface, hyperkeratosis, and papillary hypertrophy.16

The association of acanthosis nigricans and severe insulin resistance syndrome are of tremendous interest. Type A insulin resistance occurs at puberty, while type B insulin resistance syndrome occurs in older women at a mean age of 30–40 years. Type B insulin resistance syndrome patients have autoimmune diseases such as systemic lupus erythematos, Sjogren's syndrome, increased antinuclear (ANA) increased ESR and antibody to insulin receptor.17 Mild to moderate insulin resistance also exists with type II DM and obesity and can also be induced by drugs like steroids and niacin.

Insulin sensitivity index was measured with Bergmen model in 11 normal men who received incremental doses of niacin up to 2 gm/day for 2 weeks which showed a significant decrease of insulin sensitivity index from 6.72 to 0.77 to 2.47 ± 0.36 x 10^-5 min^-1/pm^1 (P < 0.0001).

The current belief that hyperinsulinemia which usually exists in modest or severe insulin resistant stimulates the skin growth by binding to IGF-I receptors or through insulin receptors that remain partially competent for signaling or through both receptors.19,20,21

The lipid profile of this patient responded very well to niacin; TG decreased to 1.4 mmol/l and HDL-C increased to 0.97 mmol/l. However, the patient developed acanthosis nigricans within three months of niacin treatment which started to improve after six weeks and completely disapaeared within twelve weeks of stopping the drug.

Oral glucose tolerance test (OGTT) was done while the patient was on niacin and showed normal response.

Insulin sensitivity index (IS) was 1.3 E-04 while the patient was on niacin and 1.6 E-04 after stopping niacin6,10,11 but the difference was not significant. The fact that the clearance of acanthosis nigricans preceded the significant improvement of insulin sensitivity in our patient doesn't go along with the expectations. The only probable explanation we found in our patient was the weight increase by 3 kg over the period through which the study was conducted, or probably niacin effect on insulin sensitivity persisted for 4.5 months.

Acanthosis nigricans was induced by niacin16 which cleared spontaneously and did not have any relation to the severity or duration of insulin resistance.

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References


ملخص:

تعرض هذه النشرة تقريراً عن حالة مريض ذكر يبلغ من العمر أربعين سنة، مصاب بارتفاع في نسبة الشحوم وانخفاض في نسبة الكولسترول ذي الكثافة العالية، وقد تجاوبت حالة هذا المريض جيداً مع العلاج بدواء النايسن. ولكن لوحظ ظهور تغيرات في جلد المريض خلال ثلاثة شهور من العلاج متمثلة في اسوداد وتثخن في الجلد وقد تم قياس مؤشر حساسية الأنسولين خلال فترة العلاج وأعيد قياسه بعد أربعة أشهر ونصف من إيقاف الدواء.

تبين من الدراسة أن التغيرات الجلدية اخفت تلقائياً، بينما استمر الانخفاض في مؤشر حساسية الأنسولين لحدهي أربعة شهور ونصف بعد إيقاف النايسن.

تدل هذه النتائج على أن التغيرات الجلدية من تثخن واسواداد ليس لها علاقة بشدة أو بمدة المقاومة لعمل الأنسولين التي تنشأ من علاج النايسن.

مفتاح الكلمات: شوكة أسود، حساسية الأنسولين.