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Review Article

Administration of insulin like growth factor I (IGF—I) lowers serum lipoprotein(a)-impact on atherosclerotic cardiovascular disease

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ABSTRACT

Insulin like growth factor I (IGF—I) secreted by the liver upon stimulation by pituitary growth hormone (GH) acts as the most important growth stimulating hormone in children. The present review presents evidence that among its additional metabolic effects, IGF-I suppresses the synthesis of lipoprotein(a) [Lp(a)], an independent risk factor for atherosclerotic cardiovascular disease. In view of this property, it is suggested that the addition of IGF-I to the armamentarium of hyperlipoproteinemia treatment should be considered.

1. Introduction

First described by Berg in 1963 [1], circulating Lipoprotein(a) [Lp (a)] is synthesized by the liver, being primarily determined by the apo(a) genotype without significant dietary or environmental influences. The levels of Lp(a) are genetically determined [2] and hyperlipoproteinemia Lp(a) runs in families with cardiovascular disease [3]. High levels of Lp (a) inhibit the natural conversion of plasminogen to plasmin contributing to a pro-prothrombotic milieu [4,5], which seems to explain its promoting effect of atherosclerotic cardiovascular disease (ASCVD) [6–8] and aortic stenosis [9]. A positive family history of premature myocardial infarction is predicted by high serum Lp(a) [2,10]. The strong genetic control of Lp(a) concentrations, associated with cardiac pathology, led to the conclusion that Lp(a) is an independent genetic risk factor for ASCVD [11]. In a previous review [12], we have shown that treatment with growth hormone (GH) increases serum Lp(a) and discussed the possible implications of this effect on the development or progression of atherosclerotic vascular disease.

It is noteworthy that despite IGF-I being the anabolic and growth enhancing effector of GH [13], it also has opposing effects such as lowering Lp(a) synthesis. Forthwith a review presenting evidence of the above.

2. IGF-I lowering effect on lipoprotein(a)

First to observe an acute reducing effect of IGF-I on Lp(a) was Zenobi et al. [14]. This was followed by several other studies in adult subjects [15–17]. The results of these studies and the effects of IGF-I on serum Lp (a) are shown in Table 1. All found an Lp(a) lowering effect by IGF-I despite low doses and short periods of administration.

Laron et al. [18] treated 10 patients with Laron syndrome, 5 children (mean age 6.7 ± 5 years) and 5 adults (mean age 32.8 years) with IGF-I (100-180 μg/kg/day sc) for 9 or 12 months and registered a 65 ± 15% decrease in serum Lp(a), more than that stated to reduce an atherosclerotic process [19]. (Table 2). It is hypothesized that the reduced hepatic production of Lp(a) by IGF-I is related to its insulin suppressing effect [20,21] It is noteworthy that these early studies were not continued.

3. Discussion

At present the determination of Lp(a) is not included in the routine evaluation of serum lipids, unless there is a history of familial hyperlipoproteinemia [2,4].

Considering the possible link between increase of Lp(a) by GH treatment [12,22] and atherosclerotic cardiovascular disease [23,24], it was suggested that levels of serum Lp(a) should be monitored during GH administration and thereafter. Despite the known link between hyperlipoproteinemia and ASCVD, no effective treatment was available until recently. High levels of serum Lp(a) do not respond to the customary treatments for hyperlipidemia such as statins. Trials with apheresis, a complicated procedure [25], and niacin [26] had only minor effects, emphasizing the need for more effective drugs.

Several biological Lp(a) lowering drugs are presently under

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Table 1
Lipoprotein(a) lowering effect by IGF-I in adults.

IGF-I treatment							
Author	Ref	Year	Subjects	Diagnosis	Dose	Duration	Effect on se Lp(a)
Zenobi	14	1993	8, 6 m, 2f	Diabetes	120 μg bid sc	5d	−48 ± 2%
Olivecrona	15	1995	11 m	Osteoporosis	80 μ/kg 1d sc	7d	−12%
Oscarsson	16	1995	10 m	Healthy	40 μg/kg/d sc	7d	−18.5 ± 5%
Bianda	17	1998	3 M 5F	Hypopits	5 μ/kg/h sc	5d	−26%

Table 2
Lipoprotein(a) Levels in Patients with Laron Syndrome Before and During IGF-I Treatment.

Patient No.	Sex	Age years	Lipoprotein(a) mg/L IGF-I (sc)			Duration of Treatment (months)
			Basal	Treatment	Difference	
1	M	0.5	72	15	57 (79.2%)	12
2	M	3.3	152	36	116 (76.3%)	12
3	M	5.1	59	25	34 (57.6%)	12
4	F	11.6	40	10	30 (75.0%)	12
5	M	14.6	41	11	30 (73.2%)	12
6	M	28.1	70	37	33 (47.1%)	9
7	F	30.0	153	92	61 (39.9%)	9
8	F	30.3	103	50	53 (51.5%)	9
9	F	35.9	35	5	30 (85.7%)	6
10	F	39.7	35	10	25 (71.4%)	6

Mean ± SD: −65.7 ± 15% ($p < 0.0001$).
Modified from Laron et.al [18].

investigation [27–32]. Among these are PCSK9 (proprotein convertase subtilisin Kexin type 9), a human monoclonal antibody. Its administration to adult patients with ASCVD decreased LDL-cholesterol as well as Lp(a) levels by 24–29% [27–29]. Tsimikis et al. [30] treated 286 patients with ASCVD by an hepatic directed antisense oligonucleotide AKCEA for 6–12 months and found that a dose of 20 mg injected subcutaneously every two weeks caused a decrease of serum Lp(a) by 72–80%. Szarek et al. [31] administered Alirocumab at four increasing doses from 5 to 20 mg by biweekly s.c. injections to 1315 adult ASCVD patients and registered a median reduction of Lp(a) of 5 mg/dL over a 4 months treatment period. In recent clinical trials Olpasiran, a small interfering RNA molecule, was injected s.c. every 12 or 24 weeks for a total of 48 weeks to patients with ASCVD and hyperlipoproteinemia. Depending on the dose there was a reduction of 44–80% of serum Lp(a) [32]. The limitation in the use of these drugs are the adverse effects and lack of long term experience [33,34]. In contradistinction to the above drugs, the experience with IGF-1 treatment over a period of 30 years and its metabolic actions are well known, as are its adverse effects related to dosage [35].

In this review we have summarized the evidence that IGF-I is an effective Lp(a) lowering drug. In view of the above, it is proposed that IGF-I be added to the armamentarium of hyperlipoproteinemia (a) treatment. As IGF-I also decreased insulin resistance [21,36], and as ASCVD is often associated with type 2 diabetes [37] the use of IGF-I would have a double beneficial effect in addition to reducing the risk for major ASCVD events.

IGF-I could also be useful in the treatment of patients with PCOS [38,39] some of whom have a high incidence of both elevated Lp(a) levels and diabetes.

4. Conclusion

The significant reduction of Lp(a) by the administration of IGF-I deserves consideration as an alternative or adjunctive treatment of hyperlipoproteinemia(a), reducing the risk or progress of atherosclerotic cardiovascular disease.

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Declaration of Competing Interest

No conflicts of interest.

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