The presentation of primary hyperparathyroidism (PHPT) has changed substantially in the last decades. Before the introduction of routine calcium measurement in most automated biochemistry serum analyzers, it usually was diagnosed after renal and bony lesions already were present. Nowadays, its presentation is practically asymptomatic. Nevertheless, the cardiovascular morbidity and mortality of mild to moderate forms of PHPT reportedly are increasing. Individuals who have mild to moderate forms of PHPT have an increased risk for enduring cardiovascular disease, arterial hypertension (HTN), left ventricular hypertrophy (LVH), myocardial and valvular calcifications, altered vascular reactivity, and cardiac conduction. Finally, they also reveal alterations in carbohydrate metabolism, insulin resistance (IR), dyslipidemia, and body composition.

Some of these disturbances (eg, LVH, alterations in carbohydrate metabolism, IR) are reversible upon surgical cure of PHPT, whereas others (eg, HTN) persist.

In hyperparathyroidism, parathyroid hormone levels (iPTH) have been reported to have significant relationships with IR as well as several proinflammatory cytokines and clotting factors, especially in secondary hyperparathyroidism in hemodialyzed patients. IR is likely to
be the most prominent and influential cardiovascular risk factor in this setting.

**Insulin resistance**

*Concept*

IR is defined as insulin’s diminished capacity to exert its biologic actions on its target tissues (ie, skeletal muscle, liver, adipose tissue) [1]. Chronic or sustained IR is the common cause for many metabolic and nonmetabolic diseases, such as type 2 diabetes mellitus (T2DM), obesity, arterial HTN, dyslipidemia, cardiovascular disease, and cancer [2,3]. In some instances (eg, obesity), IR appears as an adaptive mechanism.

Insulin is the main anabolic and anticatabolic hormone in humans. Its principal metabolic effects are exerted on skeletal muscle, liver, and adipose tissue [4].

In skeletal muscle, insulin stimulates glucose uptake and directs it toward glycogen synthesis. Moreover, insulin reduces the hepatic production of glucose and increases the rate of glycogen synthesis. Adipose tissue is much more than a simple fatty acid storage organ. Its metabolic turnover is high, and it produces many proinflammatory adipocytokines, which are hormones with autocrine and paracrine actions. Additionally, it is the tissue where insulin antilipolytic activity is exerted, and, thus, the free fatty acid liberation into circulation is inhibited.

Insulin’s antilipolytic effect accounts for more than 90% of insulin’s global actions at its physiologic concentrations. Hence, insulin stimulates glucose uptake, lipogenesis, and the triglyceride depot at the adipocytes.

**Measurement of insulin resistance**

The euglycemic hyperinsulinemic clamp [5] is the gold standard procedure for measuring IR in small patient cohorts. It is a cumbersome procedure whose cost and difficulties have prompted research toward simpler and reproducible techniques [6,7]. Most epidemiologic studies use the HOMA index (Homeostasis Model Assessment) as a surrogate marker of IR [8]. Fasting plasma glucose and insulin are measured three times at 5-minute intervals. Their mean values are used in the following equation:

\[
\text{glucose (mmol/L)} / \text{insulin (mU/L)} / 22.5.
\]

The HOMA formula provides a semiquantitative assessment of insulin sensitivity (as well as beta-cell function) based on structural mathematical modeling. Hence, a lean, healthy, young individual has an average of insulin sensitivity of 1 and a beta-cell function of around 100%. HOMA formula is applicable only to nondiabetic subjects.

There is great variability in insulin determination between different methods and laboratories. Hence, no standard insulin laboratory
determinations have been implemented internationally. Moreover, fasting insulin concentrations have a 400% to 600% variability within subjects [7,9,10]. These considerations should be kept in mind when analyzing HOMA results.

*Insulin resistance and cardiovascular risk*

Epidemiologic data clearly identify IR as an independent cardiovascular risk factor [11]. Hyperinsulinemic individuals who display normal oral glucose tolerance tests (OGTTs) tend to accumulate more cardiovascular risk factor than do those with normal fasting insulin values [12]. Clinical studies suggest that myocardial perfusion often is abnormal in individuals who do not have coronary heart disease (CHD), but who have risk factors. Moreover, the development of cardiovascular complications in individuals who have IR depends not only on the severity of IR, but also on their ability to compensate for these defects and the presence of associated comorbidities [10].

Several large epidemiologic studies identified hyperinsulinemia as an independent cardiovascular risk factor or CHD precursor: the Busselton Study in Australia [13], the Helsinki Policeman Study in Finland [14], the Paris Prospective Study in France [15], and the San Antonio Heart Study in the United States [16]. Moreover, investigators in the Bruneck Study [17], performed in Italy, observed a U-shaped curved that linked fasting plasma insulin, 2 hours post-OGTT plasma insulin with CHD. This relationship persisted after adjustment for other cardiovascular risk factors, although lost some statistical power. Finally, the Quebec Cardiovascular Study unequivocally demonstrated the fasting insulin is an independent cardiovascular risk factor after adjustment for dyslipidemia and other cardiovascular variables; nevertheless, other studies showed contradictory results [18].

IR promotes the development of atherosclerosis through different mechanisms: through changes in the lipid profile (ie, atherogenic dyslipidemia), by increasing levels of plasminogen activator inhibitor-1 and fibrinogen, by increasing vascular tone and reactivity, and by inducing endothelial dysfunction [18].

*Primary hyperparathyroidism as a cardiovascular risk factor*

PHPT is susceptible to induce an increase in the incidence and prevalence of cardiovascular disease, either by hypercalcemia itself or through the effects of parathormone. Nevertheless, there are insufficient studies to prove causality between PHPT and cardiovascular disease [19–21].

Scattered medical literature states an association between IR and PHPT. Moreover, the results are not reproducible, and the reversibility of the cardiovascular risk upon surgical correction of hypercalcemia (ie, after parathyroidectomy) remains to be proven [21]. On the contrary, the presence
of PTH-secreting adenomas is an additional cardiovascular risk factor in the natural course of CHD.

Several studies have reported a tendency toward vascular calcification in carotid intima media thickness evaluated with supra-aortic ultrasounds in PHPT. The increased carotid intima media thickness does not resolve after surgical correction of hypercalcemia [22,23].

The incidence of peri-operative cardiovascular complications is increased significantly in patients who have PHPT in the United States and Europe. Additionally, prospective studies confirmed true increases in the incidence and prevalence of cardiovascular events in these patients [21,23–26]. Conversely, no study has assessed the hypothetical link between IR and bone remodeling markers before and after surgical correction of PHPT.

The prevalence of HTN is increased in patients who have PHPT, and, occasionally, it persists after correction of hypercalcemia [27]. Conversely, fully reversible heart failure (with systolic and diastolic dysfunction) is reported in association with PHPT [28].

The relationship between PHPT and disturbances in lipid profiles (low high-density lipoprotein cholesterol levels, high triglyceride levels, and small, dense low-density lipoprotein cholesterol particles) improves upon surgical cure of PHPT [26]. The physiopathologic pathway that links hyperparathyroidism and atherogenic dyslipidemia has not been elucidated.

A few studies have reported the coincidence between the onset of T2DM and PHPT [29,30]. Indeed, the coexistence of T2DM in patients who have PHPT is an accepted criterion for urgent parathyroidectomy [31].

PHPT seems to coexist with a significant increase in glucose intolerance and T2DM prevalence. There seems to be peripheral and hepatic IR. The degree of IR correlates directly with iPTH levels [32–35]. PHPT, glucose intolerance, and IR coexist, and probable act synergistically in the natural course of cardiovascular disease [34]. Some investigators reported that IR disappeared after successful parathyroidectomy [34], and its effects on cardiovascular lesions are only transient.

The first studies that addressed the relationship between IR and PHPT appeared almost 3 decades ago [35,36], and, paradoxically, were mostly forgotten until the increase in prevalence of the IR syndrome.

IR is considered by most experts to be an epidemic condition that dramatically increases the risk for developing T2DM, CHD, stroke, and various cancers; it is estimated to affect at least one in three adults in the United States [1].

The radial artery flux and its intima media thickness were reported to be directly correlated with parathormone levels, which confirmed previous findings [37,38] on hyperparathyroidism and cardiovascular disease. Moreover, studies demonstrated the existence of endothelial dysfunction associated with PHPT and iPTH levels [38].

The availability of a full array of new markers of endothelial dysfunction—the earliest stage of atherosclerosis—and the likelihood of direct/
indirect relationships with hyperparathyroidism contribute to an increased understanding of the natural history of cardiovascular disease. These new findings will be integrated into the network of classic cardiovascular risk factors and the hypothetical relationship with genetic alterations.

Acknowledgments

The study was supported by (1) Fondo de Investigación Sanitaria (FIS) SPAIN, Grant # 01/0846 and Spanish Network CO3/08: Instituto Carlos III. Metabolism and nutrition illness and (2) Fondo de Investigación Sanitaria (FIS) SPAIN, grant number 01/0846. Spanish Network CO3/08: Instituto Carlos III. Metabolism and nutrition illness.

Further readings


References


