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Assessment of mean platelet volume (MPV) in primary hyperparathyroidism: Effects of successful parathyroidectomy on MPV levels

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Objective. A determinant of platelet function - mean platelet volume (MPV), is newly emerging risk factor for atherothrombosis. The aim of this study is to evaluate MPV in patients with primary hyperparathyroidism (PHPT) before parathyroidectomy (PTX) and six months after successful PTX in a retrospective study.

Methods. We analyzed the changes in serum biochemical, parathyroid hormone (PTH) and MPV before and six months after PTX in 66 patients with PHPT and 44 healthy controls, age- and sex-matched.

Results. Sixty-six patients (18 men, 48 women) with mean age 53.8±12.7 years were analyzed. MPV was significantly higher in the patients with PHPT before PTX than in the same group after PTX (9.26±1.20 fl vs. 7.99±0.80 fl, $p<0.0001$). MPV levels were positively correlated with PTH ($r=0.888$, $p<0.0001$), calcium ($r=0.292$, $p=0.017$) in the preoperative phase. Postoperative (after 6 months) MPV showed a significant positive correlation with postoperative PTH ($r=0.381$, $p=0.002$) and calcium levels ($r=0.324$, $p=0.008$).

Conclusions. These results suggest that subjects with PHPT lead to have increased platelet activation.

Key words: primary hyperparathyroidism, MPV, cured parathyroidectomy, PTH

Parathyroid hormone (PTH) is a key regulator of mineral metabolism, the homeostasis of calcium, phosphate, vitamin D, and bone turnover. Primary hyperparathyroidism (PHPT) is being diagnosed with increasing frequency mainly as a result of the introduction of routine serum calcium measurements. PHPT, caused by solitary parathyroid adenomas in 85% of cases and a diffuse hyperplasia in most of the remaining cases, overproduces PTH which mobilizes calcium to the blood stream (Marx 2000). Renal stones, osteoporosis and diffuse symptoms of hypercalcaemia, such as constipation, fatigue and weakness, are classical complications (Solomon et al. 1994). Patients with elevated PTH resulting from primary or secondary hyperparathyroidism have been shown to be at higher risk for cardiovascular morbidity and mortality (Garcia de la Torre et al. 2003; Andersson et al. 2004; Block et al. 2004). This increase in mortality seems to be mainly due to an overrepresentation of cardiovascular death (Hedback et al. 1990; Hedback and Oden 1998). PHPT is reported to be associated with hypertension, disturbances in the renin-angiotensin-aldosterone system,

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cardiac arrhythmia as well as structural and functional alterations in the vascular wall (Garcia de la Torre et al. 2003; Andersson et al. 2004).

Although it is controversial and the cutoff values for increased mean platelet volume (MPV) in prediction of cardiovascular risk are not clear; MPV, an indicator of platelet activation, has an important role in the pathophysiology of cardiovascular diseases (Davi and Patrono 2007). MPV is an important biological variable and larger platelets have higher thrombotic potential (Meadows and Bhatt 2007).

We aimed to evaluate levels of MPV in PHPT patients before parathyroidectomy (PTX) and six months after successful parathyroidectomy (PTX) in a retrospective study.

Materials and Methods

In this retrospective study, 66 consecutive patients with PHPT (48 female and 18 males aged 20-80 years) were recruited from Department of Endocrinology, Diskapi Training and Researching Hospital, Ankara, Turkey. The study was conducted from January 2008 to December 2011 in addition; age- and sex-matched healthy individuals were used as healthy controls (HC group). PHPT is diagnosed with elevation of PTH (or lack of suppression) in the context of hypercalcaemia. All patients underwent preoperative localization by ultrasonography and 99mTc-sestamibi scintigraphy before proceeding to parathyroid surgery. I did not apply local ethical committee for this study, because this study is retrospective. All the guidelines of Helsinki were followed.

The diagnosis of PHPT was confirmed by histopathological diagnosis based on combination of different variables, including histological pattern of the excised glands. The Third International Workshop guidelines criteria was accepted for surgical intervention. This guideline concluded that surgery is indicated in asymptomatic patients who meet any of the following conditions (Bilezikian et al. 2009):

1. Serum calcium concentration of 1.0 mg/dl (0.25 mmol/l) or more above the upper limit of normal.
2. Creatinine clearance that is reduced to <60 ml/min.
3. Bone density at the hip, lumbar spine, or distal radius that is more than 2.5 standard deviations below peak bone mass (T score < -2.5) and/or previous fragility fracture.
4. Age less than 50 years.

From all patients who underwent PTX, 61 patients had a single adenoma (chief cells), two patients had double adenoma, one patient had hyperplasia, and one patient had ectopic adenoma and one cancer. None of the 66 patients with PHPT had multiple endocrine neoplasia.

The standardized baseline screening included complete history, physical examination, skeletal radiographs, and electrocardiogram. Bone mineral density (BMD) (g/cm^2) was measured using dual-energy X-ray absorptiometry (DEXA). Osteopenia or osteoporosis were defined according to lowest measured T-score value in either spine or femoral neck. Diagnostic classification was based on the World Health Organization criteria: BMD T-score ≥ -1.0 is normal; > -2.5 and < -1.0 is low bone mass (osteopenia); and ≤ -2.5 is osteoporosis.

In this study, hypertension was defined as a mean systolic blood pressure (SBP) > 140 mmHg and or a mean diastolic blood pressure (DBP) > 90 mmHg or current treatment with antihypertensive drugs. Treatment of hypertension was defined as current use of a prescribed medication affecting blood pressure. Blood pressure in PHPT patients and controls was measured on the right arm with subject in the sitting position after at least 5 min at rest by standard mercury sphygmomanometers, and correctly sized cuffs were used. Antihypertensive drugs and doses were not changed throughout the study.

A patient with cardiovascular disease history was defined as a patient with at least one of the following health conditions: coronaropathy, myocardial ischemia or infarction, arrhythmia, stroke, aneurysm, or intermittent claudication. The upper limits for calcium and PTH serum levels were defined as <10.5 mg/dl and <65 pg/ml, respectively. Vitamin D evaluation corresponded to 25-hydroxyvitamin-D [25(OH)D] serum level (normal range, 20-100 ng/ml). Pre-operative vitamin D deficiency was defined as <20 ng/ml. Corrected calcium = serum calcium + 0.8x(4 - serum albumin).

Fasting venous blood samples were taken at baseline and after 6 months of curative PTX. Blood samples were drawn after a fasting period of 12 h. Glucose, creatinine, alanine aminotransferase and lipid profiles were determined by standard methods. Hematologic indices are evaluated from complete blood count (CBC) analysis performed by a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland). Serum urea nitrogen, creatinine, calcium, phosphorous, albumin and alkaline phosphatase (ALP) concentrations were measured by an automatic chemical analyzer (Roche Diagnostics, COBAS INTEGRA 800, Indianapolis, Indiana, USA). Normal reference values were: calcium

8.4-10.2 mg/dl, creatinine 0.5-1.2 mg/dl. Serum intact PTH was measured by a direct immunochemiluminometric assay (Siemens Healthcare Diagnostics Inc, ADVIA Centaur® XP Immunoassay System, Deerfield, USA) with normal values 10-65 pg/ml. Serum levels of 25(OH) D were measured by liquid chromatography-mass spectrometry (Siemens Healthcare Diagnostics Inc., ADVIA Centaur® XP Immunoassay System, Deerfield, USA). Cure or success of PHPT was defined as normalization of serum calcium and PTH without permanent hypoparathyroidism. Also ultrasound examinations were taken of the kidneys and gallbladder to look for calculi.

Height and body weight were measured with participants standing without shoes and heavy outer garments. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2) as a measure of relative weight. Obesity was defined as BMI > 30 kg/m^2 for both sexes.

Follow-up examinations 6 months after PTX included questionnaire, physical examination, the same blood chemistries as before operation, and blood pressure measurement.

Data are presented as mean ± standard deviation (SD). The difference in percentages in both groups was tested using chi-square test. The differences between the preoperative and postoperative mean values were evaluated using the paired or unpaired Student's t-test. Correlation analysis between MPV and different parameters was performed, calculating Pearson's or Spearman's coefficient as appropriate. Groups were compared with Mann-Whitney U test. A p value less than 0.05 (two sided test) was accepted as level of significance. Analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, Illinois).

Results

Parathyroidectomy corrected hyperparathyroidism in all cases exception one case (parathyroid cancer). Sixty-six patients were included in this study. Fourteen patients (n=14, 21.2%) presented with kidney stones and 38 (n=38, 57.6%) patients have osteoporosis. The mean age of the patients was 53.8 years (range, 20-80 years), and most of these were women (n=47, 71.2%). The mean BMI of the patients was 28.7±3.2 kg/m^2. Hypertension, history of cardiovascular disease, and diabetes was observed in 18 (27.3%), 9 (13.6%), and 7 (10.6%) patients, respectively. Pre-operative vitamin D deficiency was present in 46 patients (69.6%).

The pre- and postoperative biochemical parameters are shown in Table 1. There was a significant reduction in calcium (p<0.001), PTH (p<0.001) and ALP (p<0.001) after curative parathyroid surgery, whereas the serum 25(OH)D levels did not change significantly. However, there was no statistically significant difference between pre- and postoperative (after 6 months) fast-

Table 1

Preoperative - postoperative demographic, biochemical data and BMI in patients with primaryhyperparathyroidism and controls

	Healthy	Preoperatively	Postoperatively	p
Age (years)	51.7±11.8	52.90±13.15	52.90±13.15	0.912
Male/Female ratio	12/32	18/48	18/48	1.000
PTH (pg/ml)	38.7±9.8	274.36±191.43*#	48.83±35.15	<0.0001
Corrected Ca (mg/dl)	9.1±0.58	11.65±1.09*#	9.25±0.39	<0.0001
Phosphorus, inorganic(mg/dl)	3.4±0.71	2.32±0.53	3.80±0.42	0.040
Alkaline phosphatase (ALP)(U/l)	50.8±16.5	230.36±98.84*#	120±20	<0.0001
25-(OH)D (ng/ml)	19.43±11.7	18.7±13.4	19.1±12.5	0.543
BMI (kg/m^2)	27.4±2.9	28.7 ± 3.2	28.3±3.1	0.613
Creatinine (mg/dl)	0.56±0.21	0.86±0.22	0.58±0.19	0.030
MPV (fl)	7.56±0.62	9.15±1.14*#	7.91±0.76	<0.0001
Platelet count (x10^3/μl)	253.7±72.6	261.2±80.5	259.3±82.1	0.712

Results are presented as mean ± SD.

p<0.01 - patients with primary hyperparathyroidism (preoperative - postoperative 6th month) vs. controls

*p<0.0001 between preoperative and postoperative

#p<0.0001 between preoperative and healthy controls

There is no statistical significant parameters between postoperative and healthy controls without ALP (p=0.003).

ing plasma glucose, BMI, SBP and DBP. Preoperative serum creatinine levels were significantly higher than postoperative levels (after 6 month) (0.86 mg/dl and 0.58 mg/dl, respectively; p=0.03).

The mean T-score at the femoral neck was -1.82 (+0.30 to -4.40). The mean T-score at the total lumbal 1-4 spine was -2.36 (+1.50 to -5.20).

MPV levels were significantly higher in patients with PHPT (9.15±1.14 fl) compared to healthy volunteers (7.56±0.62 fl; p<0.0001). Six months after PTX, MPV fell significantly from 9.15±1.14 to 7.91±0.76 fl in patients with PHPT. However, no statistically significant (p=0.73) difference was observed in the MPV value between cured PTX patients (on 6th month) (7.91±0.76 fl) and the healthy controls (7.56±0.62 fl).

In preoperative phase; MPV levels were positively correlated with iPTH (r=0.888, p<0.0001), calcium (r=0.292, p=0.017), and adenoma weight (r=0.377, p=0.003). MPV levels were negatively correlated with serum phosphate (r=-0.452, p<0.0001) and total lumbar spine T score (r=-0.296, p=0.016). In contrast, no correlation was found between MPV and creatinine, vitamin D, femoral neck T-score (r=0.227, p=0.066; r=0.134, p=0.284; r=-0.192, p=0.122, respectively).

In postoperative phase (after 6 month); postoperative MPV showed a significant positive correlation with postoperative PTH (r=0.381, p=0.002) and calcium levels (r=0.324, p=0.008). No correlation was noted between MPV and serum phosphate postoperatively (r=-0.200, p=0.107). Similarly, no correlation was observed between MPV values and creatinine (r=0.135, p=0.279), and vitamin D (r=0.035, p=0.778).

Discussion

In this study, for the first time we demonstrated that MPV is significantly decreased in cured PTX. It is today well-confirmed that symptomatic PHPT has been linked with increase mortality of all causes (Lundgren et al. 2001). It has been reported that patients suffering from chronic hyperparathyroidism are more likely to have higher all-cause mortality with a standardized mortality ratio of 2.62 (Yu et al. 2011). PHPT has been associated with an increased risk for cardiovascular disease. Specifically, the incidence of coronary artery disease, valvular and myocardial calcification, left ventricular hypertrophy, cardiac conduction abnormalities and arrhythmias, cardiac functional abnormalities, carotid plaque, and endothelial dysfunction have been considered to be increased. Furthermore, increased cardiovascular risk factors such as hypertension, diabetes, and hyperinsulinism have also been observed. Malignant disorders and cardiovascular diseases such as myocardial infarction, stroke and heart failure seem to be excessively prevalent causes of death among PHPT patients (Hedback and Oden 1998; Wermers et al. 1998). The largest mortality study to date included 4461 patients that underwent surgery between 1987 and 1994, and found a highly significant increase in all-cause death as well as in cardiovascular death (risk ratio: men 1.71, 95% CI: 1.34-2.15; women 1.85; 95% CI 1.62-2.11) compared with controls (Hedback and Oden 1998). The patients were evaluated to have mild-moderate disease, but the serum calcium levels were not presented. The observed increase in mortality was independent of age and gender (Hedback et al. 1990), and was also present several years post-operatively, even though the patients were "cured" by PTX and had calcium, PTH and phosphate within the normal range (Hedback et al. 1990). Others have reported an increased risk of myocardial infarction among PHPT patients more than a year after surgery, despite normalized biochemical parameters (Vestergaard et al. 2003). The serum calcium levels were only modestly elevated at baseline (mean 1.65 mmol/l) in this study (Vestergaard et al. 2003). Conservative treatment of female PHPT patients was related to an increased risk of cardiovascular death, which could be abolished by PTX (Ogard et al. 2004). The levels of serum calcium or PTH were not presented in this study (Ogard et al. 2004). As a consequence, patients suffering from PHPT have an increased mortality that is mainly caused by cardiovascular death. The precise mechanisms underlying these associations with patients with PHPT are currently not elucidated exactly.

Patients with elevated PTH resulting from PHPT have been shown to be at higher risk for cardiovascular morbidity and mortality (Garcia de la Torre et al. 2003; Andersson et al. 2004; Hagstrom et al. 2009). Platelets play a pivotal role in atherothrombosis. Activated platelets play an important role in the pathogenesis of coronary artery disease and occlusive arterial disease (Davi and Patrono 2007). Platelets secrete and express a large number of substances that are crucial mediators of coagulation, inflammation, thrombosis, and atherosclerosis (Coppinger et al. 2004). The demonstrated ability of antiplatelet drugs to reduce cardiovascular events has reinforced the major role of platelets in the atherothrombotic process (Meadows and Bhatt 2007). Circulating platelets vary in both size and functional activity. A subpopulation of active platelets consists of

large platelets. Larger platelets are metabolically and enzymatically more active (Davi and Patrono 2007), and have greater prothombotic potential (Meadows and Bhatt 2007). Platelet size measured as MPV is possibly a simple and accurate way to estimate platelet activity (Davi and Patrono 2007; Meadows and Bhatt 2007). Elevated MPV is associated with other markers of platelet activity, including increased platelet aggregation, increased thromboxane synthesis and β-thromboglobulin release, and increased expression of adhesion molecules (Bath and Butterworth 1996). Increased MPV, reflecting increased activity of platelets, has been reported to associate with ischemic cardiac events, coronary artery calcification and predict future myocardial infarction (Chu et al. 2010; Jung et al. 2011).

Serum calcium levels have been demonstrated to be an independent predictor of mortality even within the normal range. Leifsson and Ahren (1996) explored the distribution of calcaemia in a large population-based health survey including 33346 individuals, and correlated the values to mortality during a follow-up of 10.8 years as mean. The mortality rate during the follow-up period in men less than 50 years of age was 20% higher in those with serum calcium greater than 2.45 mmol/l than in those with serum calcium less than 2.45 mmol/l. Furthermore, those with serum calcium above 2.60 mmol/l had a doubled (odds ratio=2.0) mortality rate compared with that of subjects with serum calcium below 2.60 mmol/l. This increase was principally due to cardiovascular disease. In another study (Lind et al. 1997), a cohort of 2183 males aged 50 years were investigated for serum calcium and followed-up over the next 18 years. The serum calcium levels were significantly elevated at baseline in the subjects who developed myocardial infarction when compared with the rest of the cohort (2.37±0.09 vs. 2.35±0.09 mmol/l, $p<0.03$) and Cox's proportional hazard analysis showed that serum calcium was an independent risk factor for myocardial infarction. In a more recent study of a cohort of untreated hypercalcaemic patients (serum calcium > 2.60 mmol/l) with PHPT according to biochemical criteria, the median survival time was 20 years versus 25 years in the normocalcaemic age- and sex-matched controls (Lundgren et al. 2001). The excess mortality was significant for cardiovascular disease only, and this accounted for 43% of the deaths among the patients (31% of controls). Cox's proportional hazard analysis revealed that serum calcium was independently related to the overall mortality and to the cardiovascular mortality in the patients. After adjustment for these risk factors (glucose, DBP, heart volume, age and sex), the hazard ratio for hypercalcaemia with regard to cardiovascular death was 1.72 (95% CI, 1.24-2.37; p=0.001). Similar analysis on the overall mortality revealed a hazard ratio of 1.38 (95% CI, 1.07-1.79; p=0.013). We showed that serum calcium was significantly correlated with MPV. Serum calcium and MPV levels have been reported to associate with cardiovascular mortality. We hypothesized that high serum calcium could be induced to increase MPV levels. In addition, serum calcium levels were low when MPV levels fall.

To our knowledge, MPV has not been studied in PHPT as a cardiovascular risk predictor. We evaluated MPV in PHPT before PTX and after successful PTX, and found the MPV increased in PHPT patient groups when compared with control groups and cured PTX groups. Cured PTX groups have lower MPV levels then PHPT groups. We demonstrated that MPV levels have no significant difference between cured PTX group and healthy controls. Increased MPV is associated with increased risk of myocardial infarction (MI) independent of known cardiovascular risk factors. In this study, risk of MI increased by 38% in individuals with MPV ≥7.4 vs. <7.4 fl (Klovaite et al. 2011). So, MPV levels fell in PHPT patients when cardiovascular morbidity and mortality rate would reduce.

In this study, we showed that MPV levels significantly correlated with PTH and serum calcium preoperatively, also postoperatively. To our knowledge, there are no current data on a possible effect of cured PTX on MPV. But some investigators have reported some conflicting effects of PTH in platelets.

Several mechanisms are potentially responsible for relationship between MPV and PTH in PHPT patients. First, one study has shown that acute administration of physiological concentrations of 1,34-PTH induced an increase in platelet intracellular $[Ca^{2+}]$ ($[Ca^{2+}]i$) associated with an increased arterial blood pressure in humans (Fliser et al. 1997). Moreover, a significant correlation between serum PTH and platelet $[Ca^{2+}]i$ levels has been found in normotensive patients with PHPT (Fliser et al. 1997). Cytoplasmic $[Ca^{2+}]$ levels increase in human platelets when human platelets are activation for shape-change and secretion (Salzman and Ware 1984). First, this mechanism may be induced high MPV levels in PHPT patients. Second, Emam et al. (2012) showed that inflammatory biomarkers [interleukin-6 (IL-6), hs-CRP] were higher in patients with asymptomatic PHPT than in controls. Moreover, serum PTH was significantly correlated with inflammatory biomarkers which may

suggest a subclinical inflammatory response in this group of patients. Chronic inflammation plays a pivotal role in PHPT and activated platelets (Rashid et al. 2007). Proinflammatory cytokines, such as IL-6, are involved in enhanced oxidative stress which contributes to platelet activation. Third, PTH stimulates the endothelial nitric oxide synthase (Rashid et al. 2007); furthermore PHPT induced endothelial dysfunction (Nilsson et al. 1999). Nitric oxide (NO) facilitates platelet production (Battinelli et al. 2001). The cytokines and NO produced by the dysfunctioning endothelium may stimulate the bone marrow to produce large platelets (Robinson et al. 2006). Accumulation of intracellular cytosolic calcium, leading to increased insulin resistance, has been reported in PHPT (Tassone et al. 2009). In a community-based cohort study of healthy elderly men, serum calcium was independently associated with insulin sensitivity (Hagstrom et al. 2007). Similarly, insulin resistance associated with endothelial dysfunction might trigger the same mechanisms. So platelet activation is triggered by this pathway.

In conclusion, MPV is a simple index of activated platelet and available with routine blood counts. Our data suggest that MPV is positively correlated with increased PTH and serum Calcium; however, these results should be confirmed by further studies involving a larger sample size and longer follow-up periods. Further studies on the involvement of MPV in PHPT may contribute to the evaluation of atherothrombotic risk in elderly patients with PHPT.

References

Andersson P, Rydberg E, Willenheimer R: Primary hyperparathyroidism and heart disease: a review. Eur Heart J 25, 1776-1787, 2004. http://dx.doi.org/10.1016/j.ehj.2004.07.010

Bath PM, Butterworth RJ: Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis 7, 157-161, 1996. http://dx.doi.org/10.1097/00001721-199603000-00011

Battinelli E, Willoughby SR, Foxall T, Valeri CR, Loscalzo J: Induction of platelet formation from megakaryocytoid cells by nitric oxide. Proc Natl Acad Sci USA 98, 14458-14463, 2001. http://dx.doi.org/10.1073/pnas.241427398

Bilezikian JP, Khan AA, Potts JT Jr; Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism: Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab 94, 335-339, 2009. http://dx.doi.org/10.1210/jc.2008-1763

Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15, 2208-2218, 2004. http://dx.doi.org/10.1097/01.ASN.0000133041.27682.A2

Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, Mohler ER, Reilly MP, Berger JS: Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost 8, 148-156, 2010. http://dx.doi.org/10.1111/j.1538-7836.2009.03584.x

Coppinger JA, Cagney G, Toomey S, Kislinger T, Belton O, McRedmond JP, Cahill DJ, Emili A, Fitzgerald DJ, Maguire PB: Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. Blood 103, 2096-2104, 2004. http://dx.doi.org/10.1182/blood-2003-08-2804

Davi G, Patrono C: Platelet activation and atherothrombosis. N Engl J Med357, 2482-2494, 2007. http://dx.doi.org/10.1056/NEJMra071014

Emam AA, Mousa SG, Ahmed KY, Al-Azab AA: Inflammatory biomarkers in patients with asymptomatic primary hyperparathyroidism. Med Princ Pract 21, 249-253, 2012. http://dx.doi.org/10.1159/000334588

Fliser D, Franek E, Fode P, Stefanski A, Schmitt CP, Lyons M, Ritz E: Subacute infusion of physiological doses of parathyroid hormone raises blood pressure in humans. Nephrol Dial Transplant 12, 933-938, 1997. http://dx.doi.org/10.1093/ndt/12.5.933

Garcia de la Torre N, Wass JA, Turner HE: Parathyroid adenomas and cardiovascular risk. EndocrRelat Cancer 10, 309-322,2003. http://dx.doi.org/10.1677/erc.0.0100309

Hagstrom E, Hellman P, Lundgren E, Lind L, Arnlov J: Serum calcium is independently associated with insulin sensitivity measured with euglycaemic-hyperinsulinaemic clamp in a community based cohort. Diabetologia 50, 317-324, 2007. http://dx.doi.org/10.1007/s00125-006-0532-9

Hagstrom E, Hellman P, Larsson TE, Ingelsson E, Berglund L, Sundstrom J, Melhus H, Held C, Lind L, Michaelsson K, Arnlov J: Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. Circulation 119, 2765-2771, 2009. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.808733

Hedback G, Tisell LE, Bengtsson BA, Hedman I, Oden A: Premature death in patients operated on for primary hyperparathyroidism. World J Surg 14, 829-836, 1990. http://dx.doi.org/10.1007/BF01670531

Hedback G, Oden A: Increased risk of death from primary hyperparathyroidism - an update. Eur J Clin Invest 28, 277-278, 1998.

Jung DH, Lee HR, Lee YJ, Kim JK, Park BJ, Shim JY: The association between coronary artery calcification and mean platelet volume in the general population. Platelets 22, 567-571, 2011. http://dx.doi.org/10.3109/09537104.2011.580397

Klovaite J, Benn M, Yazdanyar S, Nordestgaard BG: High platelet volume and increased risk of myocardial infarction: 39,531 participants from the general population. J Thromb Haemost 9, 49-56, 2011. http://dx.doi.org/10.1111/j.1538-7836.2010.04110.x

Leifsson BG, Ahren B: Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab 81, 2149-2153, 1996.

Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S: Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol 50, 967-973, 1997. http://dx.doi.org/10.1016/S0895-4356(97)00104-2

Lundgren E, Lind L, Palmer M, Jakobsson S, Ljunghall S, Rastad J: Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. Surgery 130, 978-985, 2001. http://dx.doi.org/10.1067/msy.2001.118377

Marx SJ: Hyperparathyroid and hypoparathyroid disorders. N Engl J Med 343, 1863-1875, 2000. http://dx.doi.org/10.1056/NEJM200012213432508

Meadows TA, Bhatt DL: Clinical aspects of platelet inhibitors and thrombus formation. Circ Res 100, 1261-1275, 2007. http://dx.doi.org/10.1161/01.RES.0000264509.36234.51

Nilsson IL, Aberg J, Rastad J, Lind L: Endothelial vasodilatory dysfunction in primary hyperparathyroidism is reversed after parathyroidectomy. Surgery 126, 1049-1055, 1999. http://dx.doi.org/10.1067/msy.2099.101422

Ogard CG, Engholm G, Almdal TP, Vestergaard H: Increased mortality in patients hospitalized with primary hyperparathyroidism during the period 1977-1993 in Denmark. World J Surg 28, 108-111, 2004. http://dx.doi.org/10.1007/s00268-003-7046-0

Rashid G, Bernheim J, Green J, Benchetrit S: Parathyroid hormone stimulates the endothelial nitric oxide synthase through protein kinase A and C pathways. Nephrol Dial Transplant 22, 2831-2837, 2007. http://dx.doi.org/10.1093/ndt/gfm269

Robinson SD, Harding SA, Cummins P, Din JN, Sarma J, Davidson I, Fox KA, Boon NA, Newby DE: Functional interplay between platelet activation and endothelial dysfunction in patients with coronary heart disease. Platelets 17, 158-162, 2006. http://dx.doi.org/10.1080/17476930500454514

Salzman EW, Ware JA: Ionized calcium as an intracellular messenger in blood platelets. Hemost Thromb 7, 177-202, 1984.

Solomon BL, Schaf M, Smallridge RC: Psychological symptoms before and after parathyroid surgery. Am J Med 96, 101-106, 1994. http://dx.doi.org/10.1016/0002-9343(94)90128-7

Tassone F, Procopio M, Gianotti L, Visconti G, Pia A, Terzolo M, Borretta G: Insulin resistance is not coupled with defective insulin secretion in primary hyperparathyroidism. Diabet Med 26, 968-973, 2009. http://dx.doi.org/10.1111/j.1464-5491.2009.02804.x

Vestergaard P, Mollerup CL, Frokjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L: Cardiovascular events before and after surgery for primary hyperparathyroidism. World J Surg 27, 216-222, 2003.

Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, O'Fallon WM, Melton LJ 3rd: Survival after the diagnosis of hyperparathyroidism: a population-based study. Am J Med 2, 115-122, 1998. http://dx.doi.org/10.1016/S0002-9343(97)00270-2

Yu N, Donnan PT, Leese GP: A record linkage study of outcomes in patients with mild primary hyperparathyroidism: The Parathyroid Epidemiology and Audit Research Study (PEARS). Clin Endocrinol (Oxf) 75, 169-176, 2011. http://dx.doi.org/10.1111/j.1365-2265.2010.03958.x