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PROINFLAMMATORY CYTOKINES IN GALLSTONE INDUCED OSTEOPOROSIS

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ABSTRACT

Objective: The aim of this study is to evaluate the Proinflammatory cytokines effects on cholilethiatic patients and evaluate levels of bone formation and bone resorption markers. Subjects and methods: one hundered patients with cholilethiasis to GOLD standards criteria were participated in this study. One hundered patients with cholilethiasis, one hundered apparently healthy subjects were selected to be a normal group for comparison. In addition, assessing the plasma levels of tumor necrosis factor alpha [TNF-α], interlukine 1[IL-1], interlukine6 [IL-6], C terminal Telopeptides of type I Collagen [CTX1] and carboxyterminal propeptide of type I procollagen [PICP] by EILISA Kits. Results: The results show that the levels of tuner necrosis factor alpha [TNF-α],interlukin 1[IL-1] , interlukine 6[IL-6], C terminal Telopeptides of type I Collagen[CTX1]and carboxyterminal propeptide of type I procollagen[PICP] elevated in serum of patients with cholilethiasis significantly as compared with control healthy groups. Conclusion: The inflammatory activity of tumor necrosis factor alpha [TNF-α], interlukine 1[IL-1] and interlukine6 [IL-6] important in develops osteoporosis in patients with cholelithiasis by its effect on bone formation and resorption markers.

KEYWORDS: Cholilethiasis, Osteoporosis, Tumor Necrosis Factor Alpha [TNF-A], Interlukine 1[IL-1], Interlukine6 [IL-6].

INTRODUCTION

Gallstone disease is one of the most common and most costly digestive diseases that require hospitalization in the United States with an estimated annual direct cost of $5.8 billion [1]. Gallstone disease is newly diagnosed in more than 1 million people annually in the United States, and cholecystectomy is performed in 700,000 cases [2]. The prevalence of gallstones has Ethnic variability, with prevalence rates of approximately 10% to 15% in The United States and Europe [3]. Cytokines play a pivotal role in the pathogenesis of cholelithiasis by driving the subsequent inflammatory response which leads to tissue damage and organ dysfunction or failure, in more severe cases [4]. Thus, an inflammatory response of a yet unknown origin in cholelithiasis may lead to the release of reactive oxygen species which might also have a potential for inducing the autodigestion of acinar cells [5]. This step induces pancreatic necrosis which triggers both recruitment and activation of inflammatory cells [4, 5]. Local recruitment and activation of inflammatory cells in cholelithiasis may lead to the production of proinflammatory cytokines, such as interleukin [IL] 6, 8, 18 and tumour necrosis factor alpha [TNF-alpha] [6- 8].

Osteoporosis is the condition in which a low bone mass and altered microarchitecture of the bone leads to increased risk of fracture [9]. Osteoporosis is categorized as either primary or secondary. Primary osteoporosis is usually due to bone loss that occurs with aging. Secondary osteoporosis is a result of medications [e.g. glucocorticoids] or diseases [e.g. malabsorption] that adversely affect skeletal health [10]. It can be caused by acceleration of bone resorption and/or deceleration of bone formation. Clinically, osteoporosis most often results from a combination of postmenopausal estrogen deficiency and age-related bone loss bone-resorbing cells [osteoclasts] and cells of the immune system both originate in the bone marrow from hematopoietic cells [11].

Osteoclasts develop from precursors of the mononuclear monocyte-macrophage cell line after stimulation by macrophage colony-stimulating factor [M-CSF] and receptor for activated nuclear factor kappa B [RANK] ligand [RANKL] [12]. Bone-forming cells [osteoblasts] are of mesenchymal origin and share a common precursor cell with adipocytes [12]. During normal bone remodeling, marrow stromal cells and osteoblasts produce RANKL, which binds to the transmembrane receptor RANK on osteoclast precursors and induces differentiation and activation [13]. This occurs through the transcription factor, nuclear-factor kappa B [NFkB], which is responsible not only for activating osteoclastogenesis but also the body's inflammatory response [14]. Both osteoclast differentiation and the inflammatory process occur via of regulation interleukin-6 [IL-6] [15]. The major role cytokines play in bone remodeling is demonstrated by the fact that receptors for the proinflammatory cytokines interleukin-1 [IL-1], IL-6, and tumor necrosis factor-alpha [TNF-α] are present on both osteoclast precursor cells and mature osteoclasts [16].

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Osteoblasts also produce osteoprotegerin [OPG], a soluble decoy receptor that blocks RANKL and maintains control of the remodeling process. OPG is vital to the success of the RANK/RANKL/OPG system of bone homeostasis [17]. At the molecular level, enhanced bone resorption and osteoporosis generally result, in part, from the overproduction of RANKL and other cytokines mediators regulating osteoclast differentiation and function [18, 19]. These include cyclooxygenase [Cox]-2, prostaglandin [PG] E2, tumor necrosis factor [TNF]-α, interleukin [IL]-1, I L-6 or IL-11. [21]. All of which lead to recruitment and differentiation of pre-osteoclasts [21].

Serum intact N-terminal propeptide of type-1 procollagen [P1NP] are considered early markers of formation, while osteocalcin, which is greatly influenced by genetics, is a later marker of osteoblastic activity [22]. Serum concentration of P1NP is directly proportional to the amount of new collagen produced by osteoblasts [23]. P1NP is useful for assessing bone turnover in postmenopausal women [24]. Accelerated osteoclastic activity increases bone turnover and is associated with low bone mass in both pre- and postmenopausal women [25]. Elevated levels of resorption markers indicate increased osteoclastic activity and a higher risk for osteoporotic hip fracture, independent of BMD [26]. Biomarker testing allows detection of metabolic change long before alterations in BMD, underscoring the need to refocus attention away from reliance solely on BMD testing. A comprehensive approach would employ biomarkers to assess risk and identify underlying disease mechanisms, including inflammation, oxidative stress, hormone imbalances, nutrient deficiencies, and malabsorption [16].

SUBJECTS & METHODS

This study was carried out at Al- Basra General Hospital from January 2012 until May2012. One hundred patients were participated in this study [90 females &10 males] the mean age of these subjects was [345±1.1]. Apparently healthy subjects were selected to participate as a normal group for comparison [control] with same age group and same sex [90female &10male] the mean age of these subjects was [35.4 ±1 .1]. Diagnosis was made by a specialized physician in surgery. The diagnosis of symptomatic gallstones depends on the presence of typical symptoms and the demonstration of stones on diagnostic imaging. An abdominal ultrasonography is the standard diagnostic test for gallstone detection. Disposable syringes and needles were used for blood collection. After 12 hours fasting, venous blood samples, about 10 ml were collected from patients before laparoscopic cholecystectomy and from healthy volunteers in plain tubes. After allowing the blood to clot at room temperature for 15 min, blood samples were centrifuged at 3000 rpm for 15 min. Fresh serum was used for the assessing the plasma levels of tumor necrosis factor alpha [TNF-α]by Enzyme linked immunosorbent assay[ELISA] KITS[27] .the interlukine 1[IL-1] , interlukine6[IL-6] assesed by Enzyme linked immunosorbent assay[ELISA] KITS[28,29].also C terminal Telopeptides of type I Collagen[CTX1]and carboxyterminal propeptide of type I procollagen[PICP] were assessed By ELISA Kits[30,31].