CHAPTER I

INTRODUCTION

1.1 Background and Significance of the Study

Diabetes mellitus (DM) refers to a group of common metabolic disorder that shares the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetic and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. Hyperglycemia leads to the chronic complications such as retinopathy, neuropathy, nephropathy, coronary artery disease, skin change, and infections that are responsible for the majority of morbidity and mortality associated with the disease (Powers, 2008).

The incidence and prevalence of DM worldwide is increasing. Total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004) due to an increase in non-insulin-dependent (type 2) DM, which represents more than 90% of all causes of diabetes. The concomitant increase in the risk factors for glucose intolerance among individuals (obesity and sedentary lifestyle) in developed and developing countries around the world suggests that diabetes will be a significant strain on health care resources for the foreseeable future (Rao and McGuire, 2004). Multiple investigators using multiple methods have developed cost-of-illness evaluations related to diabetes, and theses estimates place the total annual cost of diabetes between $291 million and $98 billion (Nachtigal and Carroll, 2004).

The evidence of type 2 DM is increased. It results from decreasing physical activity, increasing prevalence of obesity, and increasing consumption of high-caloric diets (Rao and McGuire, 2004). Furthermore, there are evidences showing that an ongoing cytokine-induced acute phase response is closely involved in the pathogenesis of type 2 DM and associated complications such as dyslipidemia and atherosclerosis (Pradhan et al., 2001; Duncan et al., 2003; Tan et al., 2003; Thorand et al., 2003; Spranger et al., 2003; Hu et al., 2004). In addition, the recent data have revealed that the plasma concentrations of inflammatory mediators increased in the insulin resistance state of obesity and type 2 DM (Pickup et al., 1997; Ford, 1999; Pickup et al., 2000; King et al., 2003).

The inflammatory mediators are soluble, diffusible molecules that act locally at the site of tissue damage and infection and at more distant sites (Štvrtinová, 1995). They include a variety of pro-inflammatory cytokines, acute phase proteins, lipid mediators, proteases, plasma-, and cell-derived growth factors (Sigal and Ron, 1994). Pro-inflammatory cytokines involve in the amplification of inflammatory process. These cytokines encompass interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α (Mantovani, 2000). Many studies showed that IL-6 was a predictor of development of type 2 DM (Pradhan et al., 2001; Duncan et al., 2003; Spranger et al., 2003; Hu et al., 2004), and the IL-6 concentrations increased in type 2 DM (Pickup et al., 1997; Pickup et al., 2000). Acute phase proteins (APPs) are the proteins whose concentrations rose or fell during the acute phase response. APPs include complements, ceruloplasmin, fibrinogen, C-reactive protein (CRP), and serum amyloid A (Sigal and Ron, 1994; Kindt, 2007). Previous studies have showed the relationship between CRP and type 2 DM (Pradhan et al., 2001; Duncan et al., 2003;

Tan et al., 2003; Thorand et al., 2003; Hu et al., 2004; Ford, 1999; King et al., 2003). Additionally, CRP is a strong predictor of future vascular events and is independent of the traditional cardiac risk factors (Heber, 2008).

The increasing of inflammatory mediators involves in inflammatory process, which is a part of immune response (Kindt et al., 2007). Individuals with DM have greater frequency and severity of infection compared to healthy people. The reasons for this include incompletely defined abnormalities in cell-mediatd immunity and phagocytic function associated with hyperglycemia. Hyperglycemia aids the colonization and growth of a variety of organisms (*Candida* and other fungal species) (Powers, 2008). Pneumonia, urinary tract infections, and skin and soft tissue infections are common in the diabetes patients (Edward et al., 1979; Wilson, 1994).

Interestingly, inflammation can be reduced by a variety of approaches including pharmacotherapy, exercise, and diet (Farmer, 2008). Several drugs (aspirin, rosiglitazone, captopril, ramipril, and pravastatin) with anti-inflammatory properties can lower inflammatory mediators and reduce the development of type 2 DM (Hansson et al., 1999; Hundal et al., 2002; Haffner et al., 2002; Sjöholm and Nyström, 2006). Exercise and weight reduction play a role in decreasing CRP levels in patients with impaired glucose tolerance (Orchard et al., 2005). In addition, dietary supplements (alpha tocopherol, probiotic microbes, alpha-linolenic acid, flaxseed-derived lignan, soy protein, and whey protein) was found to reduce inflammatory mediators (Devaraj and Jialal, 2000; Gill et al., 2001; Rallidis et al., 2003; Pan et al., 2007; Li et al., 2005).

Whey protein is a protein complex derived from milk. Milk contains two primary sources of protein, the casiens and whey. The casien is the protein

responsible for making curds, while whey remains in an aqueous environment. Liquid whey processed in advance technologies have resulted in several different finished whey protein products, such as whey protein concentrate (WPC), whey protein isolate (WPI) and whey protein hydrolysate (WPH). The biological components of whey protein including beta-lactoglobulin (β-LG), alpha-lactalbumin (α-LA), bovine serum albumin (BSA), immunoglobulins (Ig), lactoferrin (LF), lactoperoxidase, and glycomacropeptides (GMP) demonstrated wide ranges of immune system modulation such as anti-inflammation (Mattsby-Baltzer et al., 1996; Cross and Gill, 1999; Oben et al., 2008), lymphocyte proliferation (Mercier et al., 2004), cytokine secretion (Saint-Sauveur et al., 2007), improved phagocytosis (Rutherfurd-Markwick and Gill, 2005b), and antibody response (Low et al., 2003; Rutherfurd-Markwick and Gill, 2005a; Rutherfurd-Markwick and Gill, 2005b). There were also the studies about the effect of whey protein on inflammatory mediator reduction. Oben et al. (2008) found that the healthy males had significant decreased hs-CRP level after taking 50 g WPC containing either 2.5 g or 5 g of a proteolytic enzyme. Mattsby-Baltzer et al. (1996) found that LF in whey protein inhibited IL-6 release from monocytic cell line when stimulated with lipopolysaccharide (LPS). This result suggested an anti-inflammatory activity of LF.

Although whey protein is usually well tolerated by most individuals, there was the report about the adverse effects of whey protein supplementation. It was minor gastrointestinal disturbances after whey protein consumption (Marshall, 2004). No severe adverse effect was noted following administration of whey protein in diabetic patients (Frid et al., 2005).

With several effects on immune system, whey protein may be advantage for diabetic patients. However, the effects of whey protein in type 2 DM are rarely investigated. Therefore, this study was designed to investigate the effect of whey protein supplementation on inflammatory mediators in type 2 DM.

1.2 Objectives of the Study

1. To assess inflammatory mediators in type 2 diabetic outpatients at Public Health Center 66, Health Department, Bangkok Metropolitan Administration
2. To investigate the effect of whey protein supplementation on inflammatory mediators in type 2 DM

1.3 Benefits of the Study

This study provides information about inflammatory mediators in type 2 DM and the effect of whey protein supplementation on inflammatory mediators in type 2 DM. The findings will be beneficial for consideration of whey protein supplementation in type 2 diabetic patients.