Higher circulating adiponectins may lower the risk of metabolic disorder even in higher C-reactive protein concentrations : non-diabetic Korean men

Hyun Jin Choi

The Graduate School
Yonsei University
Graduate Program in Science for Aging
Aging and Clinical Nutrition

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Hyun Jin Choi

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This certifies that the master's thesis of

Hyun Jin Choi is approved.

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Thesis Supervisor : Jong Ho Lee

_____

Thesis Committee Member : Yangsoo Jang

_____

Thesis Committee Member : Oh Yoen Kim

The Graduate School

Yonsei University

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감사의 글

지난 2년 동안 대학원에서의 생활은 저에게 어떠한 시간보다도 많은 것을 배우고 느낀 값진 시간이었습니다. 논문이 완성되기까지 많은 가르침과 도움을 주시고 따뜻한 격려를 아끼지 않으신 많은 분들께 부족하나마 지면을 통해 그 감사의 마음을 전합니다.

지금까지 부족한 저에게 임상영양학에 대한 많은 배움의 기회와 가르침을 주신 이종호 교수님께 진심으로 감사드립니다. 많이 바쁘신 와중에도 끊임없는 관심과 애정으로 지도해주시고 학문에 대한 열의를 일깨워주시는 장양수 교수님께도 깊은 감사를 드립니다. 항상 멋진 강의로 학문에 대한 호기심을 자극하게끔 해주시는 조홍근 교수님, 언제나 따뜻하게 지켜봐 주시고 가르쳐주시는 정지형 교수님께도 감사의 마음을 전합니다. 학부 생활 동안 영양학이라는 학문에 대해 눈을 뜨게 해주시고 꿈을 가질 수 있게 많은 가르침을 주신 김영옥 교수님, 윤석권 교수님, 장은재 교수님, 김명애 교수님께도 마음속 깊이 감사드립니다.

616호에 있을 때 보다 많이 보지는 못하지만 무슨 일이 있든 기댈 수 있었고 많은 도움을 주신 지숙언니, 언제나 바쁜 와중에도 인자한 모습으로 격려를 아끼지 않았던 오연언니, 많은 이야기를 나누지는 못했지만 항상 만날 때 마다 웃는 얼굴로 힘을 주었던 수정언니, 아이 때문에 잠시 떨어져 있었지만 처음했던 스터디에서 많은 것을 배우게 해주신 지영언니, 노과연에 없어서는 안될 큰 존재인 정임언니에게 감사의 마음을 전합니다.

2년 동안 항상 얼굴 보면서 좋은 일, 힘든 일 함께 보내면서 미운정, 고운정 다 들었던 너무나도 소중한 인연인 우리 연구실 식구들에게 감사의 마음을 전합니다. 연구실 생활 동안에 가장 많이 가르침을 받았던 큰혜진언니, 언제가 바쁘지만 웃어주고 힘들 때마다 격려해주던 예정언니, 항상 짓궂게 굴어도 언제나 좋은 얼굴로 대해주던 윤지숙언니, 노과연 박사로 열정을 다하는 현양언니, 언니들 덕분에 힘든 일도 잘 견디고 많이 배우면서 연구실 생활 할 수 있었고 고맙습니다. 사회로 나아 각자의 위치에서 멋지게 활약하고 있는 선배들인 엄한 선배였고 처음 스터디 때 많은 것을 가르쳐 준 여진언니, 항상 바른 모습을 보여주었던 작은혜진언니, 장난꾸러기 같았던 수경언니, 언제나 내가 하는 일에 있어서 많은 도움과 지도를 아끼지 않는 슬희언니, 3학기 동안 철없고 개성강한 후배 때문에 많이 속썩었을 은정언니, 현지언니, 승은언니, 유란언니에게도 고마움을 전합니다. 나이 어리고 까다로운 성격의 선배 때문에 많이 힘들었을 3학기 후배들. 처음 스터디 생활부터 힘들었을 3학기 맞언니 박수현언니, 거의 3학기 내내 일산병원에서 동거 동락했던 미진언니, 항상 다른 일 때문에 바쁜 유미언니, 나의 실험 파트너 민지언니, 그리고 유일한 나보다 어린 진정한 후배인 스터디, 실험, 수업시간 내내 나에게 가장 많은 괴롭힘을 당했던 정현이, 이 모두에게 깊은 감사의 마음과 앞으로 남은 연구실 생활 후회 없이 보낼 수 있기를 바랍니다. 같이 한 시간은 얼마 안되지만 너무나 이쁘고 정이 많이 갔던 1학기 후배들. 들어오자마자 어려운 스터디와 까다로운 스터디 헤드 때문에 힘들었을 미란이, 착한 심성을 가진 소의, 맨날 장난쳐도 웃으면서 받아주던 시내, 소심한 남자친구 때문에 고민하던 소연이, 귀염둥이 막내 효희, 사투리 때문에 많이 구박 당했던 멋진 패션의 여진이와 든든한 같은 스터디 멤버인 주연이, 무뚝뚝하지만 맘 따뜻한 주영이와 1학기는 아니지만 1학기 후배 같은 내숭쟁이 승현이에게도 항상 웃음와 즐거움을 주어서 고마웠고 앞으로의 힘든 일도 즐거운 일도 지혜롭게 꿈을 향해서 헤쳐나가길 바랍니다. 2년 동안 많은 일들을 같이 겪으면서 나 때문에 맘상한 일도 많았을 테지만 항상 내편이 되어주었던 영원한 나의 동반자 우리 동기들! 노과연 단짝이자 합체하면 같이 헤쳐나가

지 못할 일이 없었던 오수현 언니, 철없는 동생에게 항상 바른 길을 안내해주던 우리 동기의 맞언니 계영언니, 나의 성격과 정반대의 모습으로 차분하게 자기 일을 잘해나가는 친구이자 동기인 진경이에게 감사의 마음을 전하며 졸업 후에 모두에게 좋은 일만 있고 영원히 행복하기를 바랍니다. 이른 아침마다 변함없는 미소를 보여주시던 김문경 선생님과 김희경 선생님에게도 감사드립니다.

함께 수업 들으면서 좋은 인연이 되어주신 노과연 식구들에게도 감사의 마음을 전합니다. 언제나 인자하신 모습으로 모든 일에 아낌없는 뒷받침 해주시는 신경균 선생님, 너무나 젠틀하신 멋진 홍창형 선생님, 자주는 못 보지만 볼 때마다 따뜻하게 대해주는 신영언니, 우리 연구실 스터디의 다크호스 김경철 선생님, 회식 때마다 우리에게 웃음을 선사해주시던 조석현 선생님, 올해 이쁜 딸의 아빠가 되신 행복하신 이기호 선생님, 한 학기밖에 얼굴을 못봐서 아쉬운 엉뚱하신 배태기 선생님, 너무나 여성스러우신 차승헌 선생님, 못나고 버릇없는 후배 때문에 힘들었을 봉준오빠, 너무나 어른스러운 동생같지 않은 후배 강원이, 특별한 인상을 남기고 군대로 떠나버린 태원이, 동갑이라서 어려울 텐데 항상 편하게 해주는 신비함을 가진 수혁이, 너무나 말없는 많이 친해지지 못해서 아쉬운 승원오빠에게도 진심 어린 감사의 마음을 전합니다.

언제나 못나고 성격강한 내편이 되어주는 나의 소중한 친구들! 항상 내 입장에서 생각해주고 나를 참 편하게 해주는 맘 착하고 이쁜 쥬얼리 디자이너 선영이, 멋진 커리어 우먼이 된 참한 친구 혜인이, 언제나 소녀 같은 선생님인 선숙이, 10년 넘게 좋은 친구로 나에게 힘을 주는 지은이, 언제나 씩씩하고 삶의 모범이 되는 친구인 기정이에게 고마운 마음을 전하며 앞으로 모두에게 좋고 행복한 일만 가득하길 바라며 영원히 좋은 친구로 서로에게 힘이 되었으면 좋겠습니다.

대학원 생활의 시작부터 지금까지 힘들 때마다 옆에서 버팀목이 되어주며 항상 나

에게 최선을 다해주었고 공부하는데도 많은 도움을 주었던 남자친구 인광오빠에게 고마움을 전하며 앞으로도 함께 영원히 행복하길 바랍니다.

마지막으로 가족들께 감사의 마음을 전합니다. 부족하고 고집 센 딸의 모든 것을 이해해주시고 무엇을 하던지 믿어주시는 아빠, 엄마께 진심으로 존경과 사랑의 마음을 전합니다. 지금은 많이 철없는 어린 동생이지만 소중한 나의 동생에게도 앞으로의 미래에 꿈을 이루기를 바라며 감사의 마음을 전합니다. 세상 누구보다 소중한 가족에게 사랑의 마음과 함께 이 작은 결실을 바칩니다.

2006년 7월

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ABSTRACT

Higher circulating adiponectins may lower the risk of metabolic disorder even in higher C-reactive protein concentrations : non-diabetic Korean men

Hyun Jin Choi
Graduate Program Science for Aging
The Graduate School
Yonsei University

Objective: Plasma adiponectin and C-reactive protein (CRP) are related to metabolic disorder such as obesity, diabetes mellitus (DM) or cardiovascular disease (CVD). We investigated the associate effect of plasma adiponectin and CRP on metabolic disorder in nondiabetic Korean men.

Methods: Nondiabetic Korean men (21-70yrs, body mass index: 18.5~33.9kg/m^2, n=658) were subdivided into four groups according to median concentrations of adiponectin (4.36μg/mL) and CRP (0.36μg/mL); higher adiponectin/lower CRP (n=172), higher adiponectin/higher CRP (n=159), lower adiponectin/lower CRP (n=153), lower adiponectin/higher CRP (n=174). We measured anthropometric parameters, lipid profiles, insulin resistance (IR), plasma adiponectin, plasma CRP, LDL particle size and coagulation markers.

Results: Regardless of plasma CRP concentrations, subjects with higher adiponectin concentrations had lower serum triglyceride, lower atherogenic index, lower IR, higher HDL cholesterol and higher LDL particle size than those with lower adiponectin before (all of p-values <0.001) and after the adjusting for age, body mass index (BMI), cigarette smoking and alcohol drinking (all of p-values<0.01). We also observed the associate effect of adiponectin and CRP on metabolic disorder; subjects with lower adiponectin/higher CRP not only had highest fasting insulin, higher IR, higher platelets and lowest LDL particle size (p<0.001) among four groups before and after the adjustment, but also had higher risk of metabolic syndrome as compared with higher adiponectin/lower CRP groups before [OR:2.994 (CIs:1.739-5.154) p<0.001] and after adjustment [OR:2.253 (CIs:1.085-4.677) p=0.029]

Conclusion: we found the associate effect of plasma adiponectin and CRP on metabolic disorder but in non-severe obesity and non-diabetic states, maintaining higher adiponectin concentrations may relatively reduce the risk of metabolic syndrome even though plasma CRP concentrations are high.

Key Word: adiponectin, C-reactive protein, non-diabetic, metabolic syndrome

1. INTRODUCTION

Circulating adiponectins are inversely correlated with adiposity, fasting insulin and serum triglyceride, and positively correlated with HDL-cholesterol and LDL particle size (1-4). Hypoadiponectinaemia has been found in obese subjects and patients with type2 diabetes or cardiovascular disease (CVD) compared with healthy subjects (5-7).

Also the inflammation markers, themselves have been reported to play an important role in metabolic syndrome (MetS) and CVD (8-10). Particularly, plasma C-reactive proteins (CRPs) responding to tissue injury, autoimmune disorders or microbial infection (11-13) induce the production of inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α (14-16) and expression of tissue factor playing an important role in coagulation (17), and promote the uptake of oxidized-LDL (15,16).

Many studies have reported the negative relationship between plasma adiponectin and CRP in obesity, MetS or CVD. Clinical human studies reported that low concentrations of adiponectin in obesity were negatively correlated with systemic inflammatory markers (18,19) and adiponectin may regulate inflammatory response (20,21). In vitro experiments showed that adiponectin suppressed the production of inflammatory markers (22,23) and induced anti-inflammatory mediator (22,24,25).

Thus, adiponectin concentrations are major mediator of MetS, diabetes or CVD (5,26,27) through its multiple protective roles as anti-diabetic, anti-atherosclerotic, and anti-inflammatory factor.

However, there were few researches for the associated effect of plasma adiponectin and CRP on metabolic disorder. Therefore, this study aimed to investigate the anthropometric and biochemical markers related to the risk of metabolic disorder in non-diabetic Korean men according to plasma concentrations of both adiponectin and CRP.

2. BACKGROUND

2.1. Adiponectin

Recent research has shown that adipose tissue is not simply an inert storage depot for lipids but also represent an important and very active endocrine organ that produces a number of hormones and other substances with significant roles in the regulation of insulin sensitivity, the integration of endocrine, metabolic, and inflammatory signals for the control of energy homeostasis (38, 50).

Adiponectin is a novel, adipose-specific protein belonging the collectin family. The protein is present abundantly the circulation, accounting for ≈ 0.01% of total plasma protein (5). Unlike many of the other "adipokines" such as tumour necrosis factor-α (TNF-α), leptin and resistin that increase with adiposity, circulating adiponectin concentrations are reduced in individuals who are obese, have cardiovascular disease or Type 2 diabetes (2).

Adiponectin is abundantly present in human plasma. Adiponectin circulates at high concentrations ranging from 2 to 30mg/L, which is 10^3 higher than the concentration of other major hormones (e.g. leptin and cortisone), and 10^6 higher than those of most inflammatory cytokines (e.g. tumor necrosis factor (TNF)-α and interleukin (IL)-6).

Adiponectin is also known as gelatin binding protein-28 (GBP28) in humans, adipocyte complement-related protein of 30 kilodalton (Acrp30) or AdipoQ in mice (38). The human adiponectin gene that is encoded by apM1 mRNA, is located on chromosome 3q27 and it codes for a 244 amino acid polypeptide with a signal sequence (42). The apM1 gene product was a kind of soluble matrix protein (1). 244 amino acid residues containing a short noncollagenous N-termianl segment followed by a collagen-like sequence. Adiponectin is presumed to form a homotrimeric subunit with a collagen-like triple-helical structure and circulate through the body as a multimer of trimers (23). Adiponectin gene consists of three exons and two introns (1).

While all of the currently known adipose-derived hormones related to insulin resistance are increased by obesity, adiponectin production and concentrations actually decreased in obese subjects (50).

Adiponectin levels are also significantly lower in patients with coronary artery disease than in matched control subjects, and in patients with type 2 diabetes mellitus and in patients with coronary artery disease (CAD) suggesting a possible association of reduced adiponectin in vasculopathic states (41). The fact that obesity is the state of adiponectin deficiency makes this hormone a very tempting target for possibility that adiponectin treatment may improve obesity-related insulin resistance and atherosclerosis (50).

Recent reports suggested that adiponectin may have anti-inflammatory and anti-

atherogenic properties. Moreover, a recent study demonstrated that the C-terminal globular domain of adiponectin protects against atherosclerosis.

There are growing evidence that adiponectin has multiple beneficial effects on metabolism.

2.2. Adiponectin, Obesity and Insulin Resistance

Obesity, defined as an accumulation of excess body fat frequently accompanies insulin resistance, hypertension, dyslipoproteinemia and vascular diseases and a major health problem in the industrialized countries (1).

The increasing mass of white adipose tissue in obesity reduces adiponectin protein synthesis by a feedback inhibition. Hypoadiponectinemia may contribute to insulin resistance and accelerated atherogenesis associated with obesity (43).

Type 2 diabetes is characterized by obesity-related insulin resistance. Although most glucose uptake occurs in skeletal muscle, considerable evidence suggests a role in this uptake for adiponectin. Low adiponectin levels precede and predict type 2 diabetes, and increasing levels of plasma adiponectin improve insulin sensitivity (45). Insulin resistance induced by an excess of adipose tissue is one of the major risk factor for diabetes and cardiovascular disease (34).

A recent study has shown that elevated adiponectin levels are associated with a

substantially reduced risk of type 2 diabetes in adults, after adjusting for sex, age, BMI, WHR, alcohol consumption, smoking, educational status and glycosylated hemoglobin A1c (45).

The effect of adiponectin in increasing insulin sensitivity and decreasing plasma TG and suggest that adiponectin, in humans and animals, has insulin sensitivity-inducing properties.

Administration of full-length or globular adiponectin in mice increase AMPK-dependent phosphorylation in skeletal muscle; in the liver, this activation is achieved only with full-length form. Activation of AMPK is required for phosphorylation of acetyl CoA carboxylase(ACC), fatty acid oxidation, glucose uptake and muscle cell lactate production, phosphorylation of ACC and reduced expression of both phosphoenol pyruvate carboxykinase(PEPCK) and glucose-6-phosphatase(G6Pase) in the liver of mice receiving adiponectin. Expression of the receptor Adipo R1 in muscle cell is associated with increased phosphorylation of AMPK, ACC and p38 mitogen activated kinase(MAPK), whilst in liver cells there is an increase in phosphorylation of AMPK and ACC.

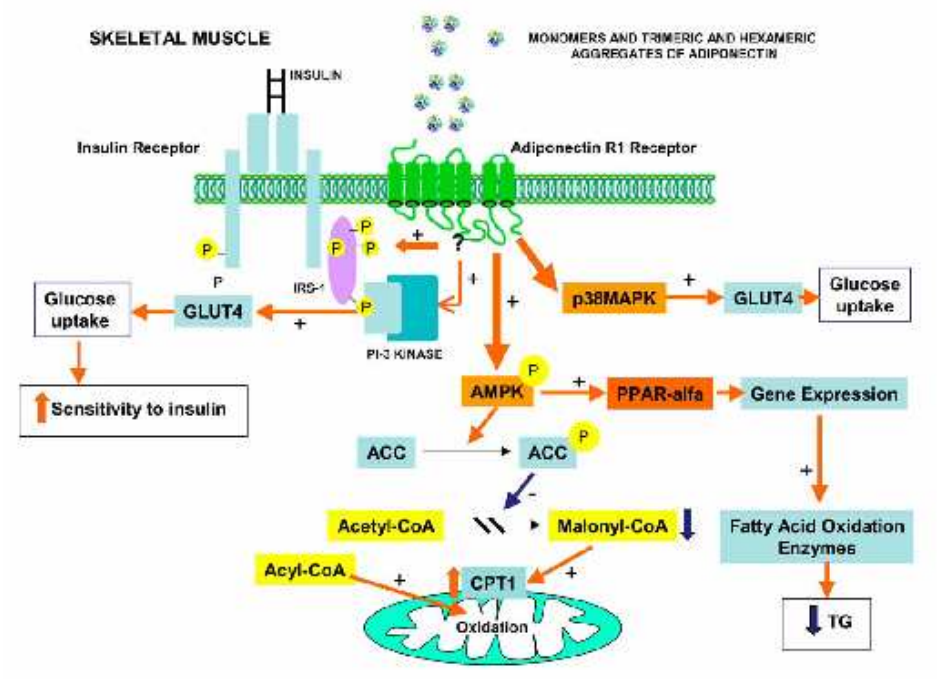

Fig 1. Model for molecular action of adiponectin in muscle. (adapted from 45)

Similarly, adipocyte-receptor interaction increases the activity of PPAR-α, a transcription factor expressed in the liver, which plays an essential role in regulating fatty acid oxidation. To summarize the molecular mechanism by which adiponectin increase insulin sensitivity appears to be related to the activation of AMP kinase which directly enhances glucose uptake in muscle and increases fatty acid oxidation both in muscle and liver, as well as activated the transduction signal cascade of insulin in both tissues (30, 46, 47).

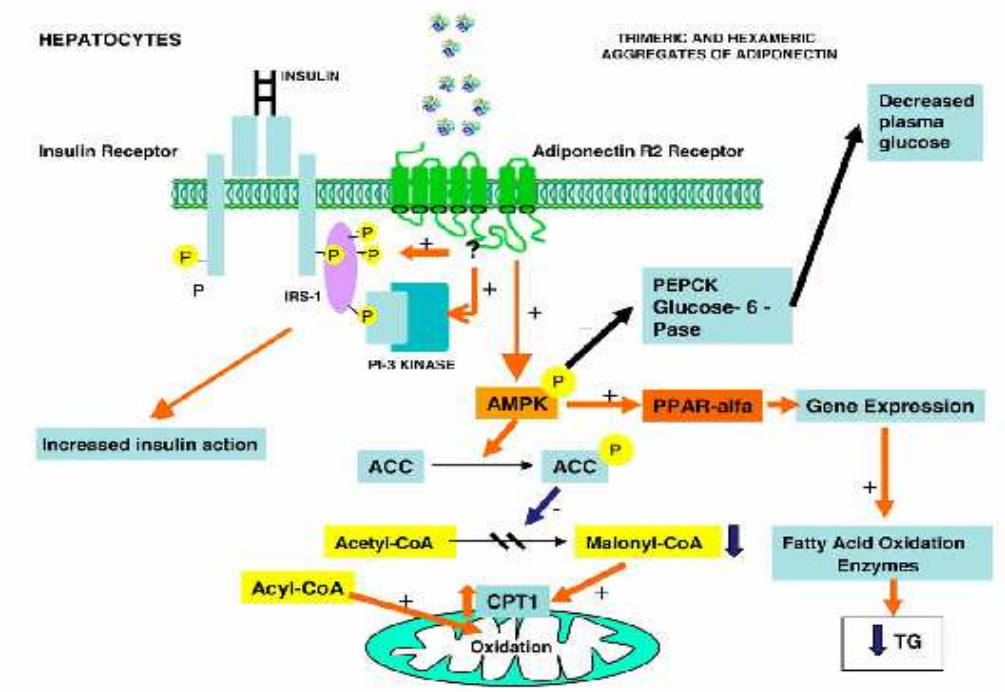

Fig 2. Model for molecular action of adiponectin in liver. (adapted from 45)

2.3. Adiponectin and Cardiovascular Disease

The growing epidemic of cardiovascular disease in developed countries and the third world is closely associated with an increased prevalence of insulin resistance and type 2 diabetes due to excess body weight and sedentary lifestyles. Insulin resistance, a failure of circulating insulin to elicit its expected responses in glucose and lipid metabolism, plays a key role in the development of the metabolic syndrome, a complex set of risk factors, including hyperinsulinemia, hypertension, glucose intolerance, and dyslipidemia, that dramatically heightens cardiovascular risk. The pathogenic relationships among obesity the metabolic syndrome and its cardiovascular complications, however, remain poorly understood, and intensive research efforts are underway to elucidate the mechanisms by which excess adiposity, especially in visceral dysfunction (41). Atherosclerotic cellular changes consist of basically the following 3 cellular phenomena: monocyte adhesion to endothelial cells by the expression of adhesion molecules, oxidized LDL uptake up macrophages through scavenger receptors, and proliferation of migrated smooth muscle cells by the action of platelet-derived growth factors or heparin-binding endothelial growth factor-like growth factor (27). Adiponectin influences various aspects of endothelial function (48). Physiological concentrations of adiponectin inhibit TNF-α-induced monocyte adhesion and expression of endothelial-leukocyte adhesion molecule-1(E-selectin), vascular cell adhesion molecule-1(VCAM-1), and intracellular adhesion molecule-1(ICAM-1) in

human aortic endothelial cells in vitro (48). It has been suggested that the intracellular signal by which adiponectin suppressed adhesion molecule expression in inhibition of endothelial NF-kB signaling through the activation of cAMP protein kinase A. Adiponectin suppressed macrophage to foam cell formation through the inhibition of class A macrophage scavenger receptor (SR-A).

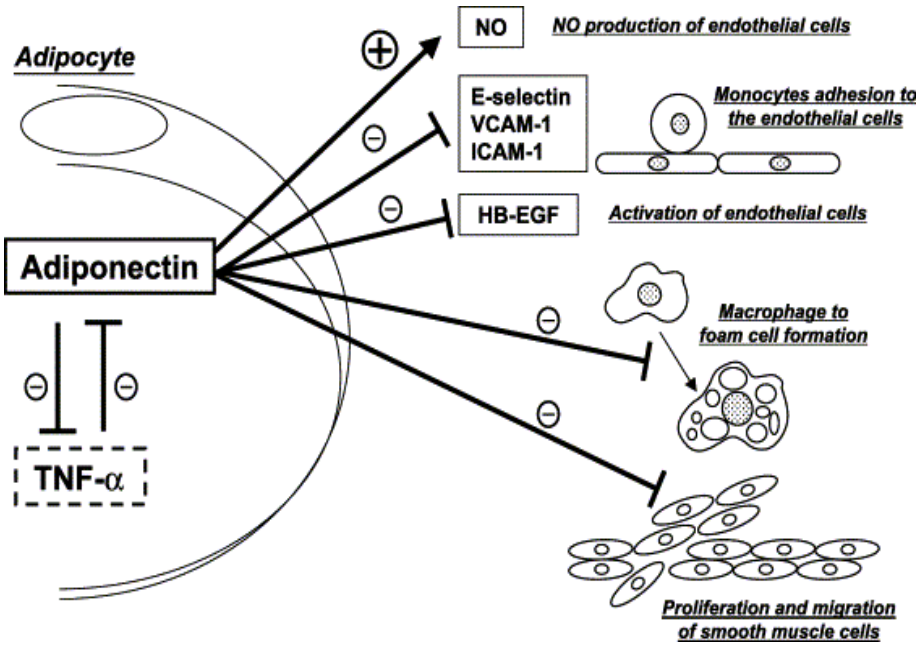

Fig 3. Adiponectin in the pathogenesis of atherosclerosis. (adapted from 34)

In addition adiponectin has inhibitory effects on the proliferation of myelomonocytic lineage cells, and on the function of matured macrophages, such as

phagocytosis and TNF-α production. Moreover, adiponectin suppressed the proliferation and migration of smooth muscle cells induced by platelet-derived growth factor(PDGF)-BB through binding with PDGG-BB directly, and inhibit p42/44 extracellular signal related kinase (ERK) phosphorylation in PDGF-BB-stimulated smooth muscle cells (34). And a recent report demonstrated that adiponectin has the direct action of stimulating the production of nitric oxide (NO) in endothelial cells (49).

Adiponectin might be likened firefighters who put out the fire of the vascular walls while it is still small. When the plasma levels of adiponectin are decreased in the subjects with visceral fat accumulation, the small fire may become bigger and bigger because of the shortage of firefighters (27).

The reduced circulating levels of adiponectin in visceral adiposity are now known to contribute not only to insulin resistance and dysglycemia, but also to the endothelial vascular dysfunction that is characteristic of the metabolic syndrome.

2.4. C-reactive protein(CRP)

In 1930 interest was focused on these changes by the discovery of C-reactive protein (so named because it reacted with the pneumococcal C-polysaccharide) in the plasma of patients during the acute phase of pneumococcal pneumonia (51, 63, 75).

The acute-phase response consists of a set of complex metabolic changes during inflammatory states, which include fever, leukocytosis, alterations in lipid and

carbohydrate metabolism, and changes in synthesis of several plasma proteins referred to as acute-phase proteins (APPs) (16). A major human APP that has been investigated extensively is Creactive protein (CRP) (16).

C-reactive protein (CRP) is a normal plasma protein that belongs to the evolutionary ancient and highly conserved pentraxin family (53, 61, 62). Its plasma level increases 100- to 1,000-fold within 24 to 72 hours in a cytokine-mediated response to most forms of tissue injury, infection, and inflammation (13, 61). The magnitude of the increases varies from about 50 percent in the case of ceruloplasmin and several complement components to as much as 1000-fold in the case of C-reactive protein and serum amyloid A, the plasma precursor of amyloid A (the principal constituent of secondary amyloid deposits). Following removal of the inflammatory stimulus, CRP levels decline rapidly (13).

CRP has been observed inside human atherosclerotic lesions and some experiments described that this pentraxin could interact with lipoproteins (mainly oxidized and modified LDL), promote inflammatory activation of monocytes, smooth muscle cells (SMC) and EC, and enhance thrombotic complications (60).

CRP occurs in at least 2 different conformationally distinct forms, native CRP (nCRP) and modified CRP (mCRP) (61).

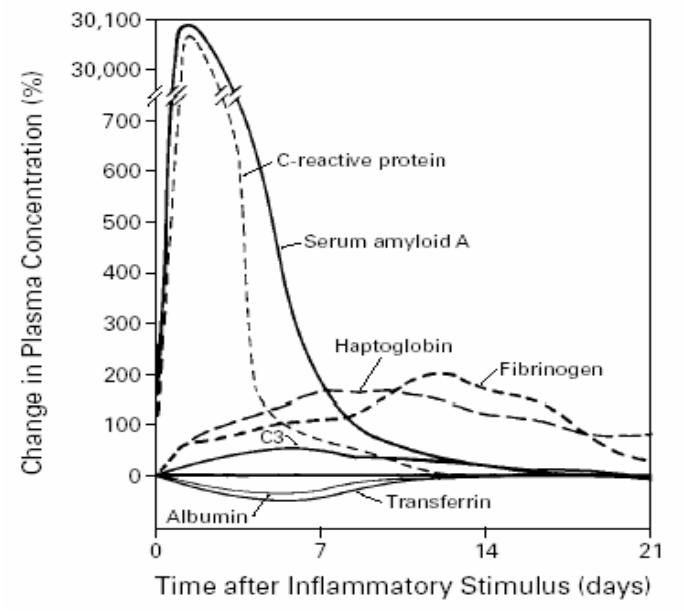

Fig 4. Characteristic Patterns of Change in Plasma Concentration of Some Acute-phase Proteins after a Moderate Inflammatory Stimulus. (adapted from 51)

2.4.1. Native CRP

nCRP is a cyclic pentameric protein of five identical nonglycosylated subunits of 206 amino acids, each with a molecular mass of 24kDa, that are noncovalently bound to form the mature CRP molecule (13, 61, 63). 206 amino acid residues, arranged symmetrically around a central pore (82). It is a highly soluble serum protein that shows calcium-dependent affinity for phosphate monoesters, in particular, phosphocholine. Other intrinsic ligands include native and modified plasma

lipoproteins, damaged cell membranes, small ribonucleoprotein particles, apoptotic cells, and fibronectin (53, 61).

When bound to these ligands, CRP is recognized by C1q, leading to activation of the classical complement pathway. In addition, bound CRP may bind factor H and thereby regulates alternative-pathway amplification and C5 convertases (61). In serum, CRP levels increase rapidly after a single stimulus. The half-life of CRP is approximately 19 hours and appears to be similar under physiological and pathological conditions (61, 63). Native CRP is used in daily clinical practice and represents the classical acute-phase reactant. Median CRP level in middle-aged Americans is approximately 1.5 mg/L (61).

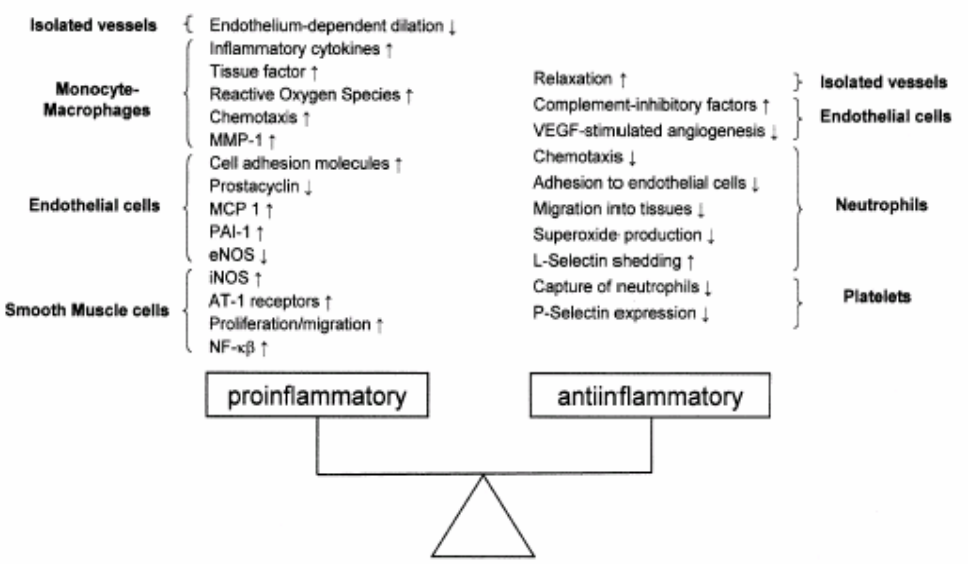

Fig 5. Potential proinflammatory and anti-inflammatory effects of nCRP on monocytes/ macrophages, neutrophils, endothelial and vascular smooth muscle cells, platelets, and isolated vessels. (adapted from 51)

2.4.2. Modified CRP

nCRP can undergo subunit dissociation into individual monomeric units, eg, when associating with a cell membrane (61). Such conformational rearrangement significantly modifies CRP structure, solubility, and antigenicity. This conformationally distinct form of CRP is referred to as "modified, monomeric," or mCRP. Like nCRP, mCRP also is a naturally occurring stable protein, although not detectable in serum. mCRP is characterized by decreased solubility and a tendency to self-aggregate, thus

representing the tissue-bound form of CRP. mCRP epitopes can be expressed from nCRP by treatment with urea chelation, acid, or heat or by direct immobilization onto polystyrene plates (61). Antigens that cross-react with an anti-mCRP antibody have been described in human monocyte/macrophages, epithelial cells of the respiratory tract, and fibrous tissues of normal blood vessel intima (61).

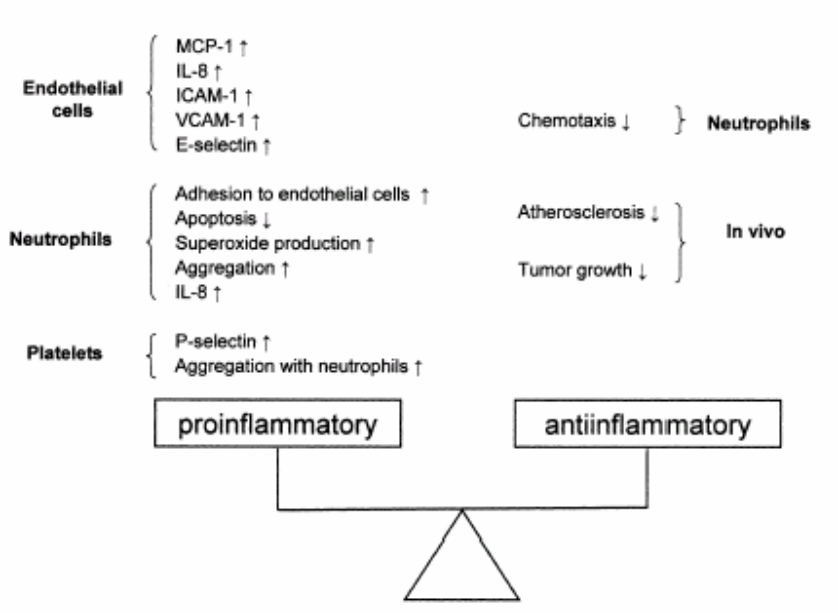

Fig 6. Summary of proin-flammatory and anti-inflammatory effects of mCRP on endothelial cells, neutrophils, and platelets and in 2 murine in vivo models. (adapted from 51)

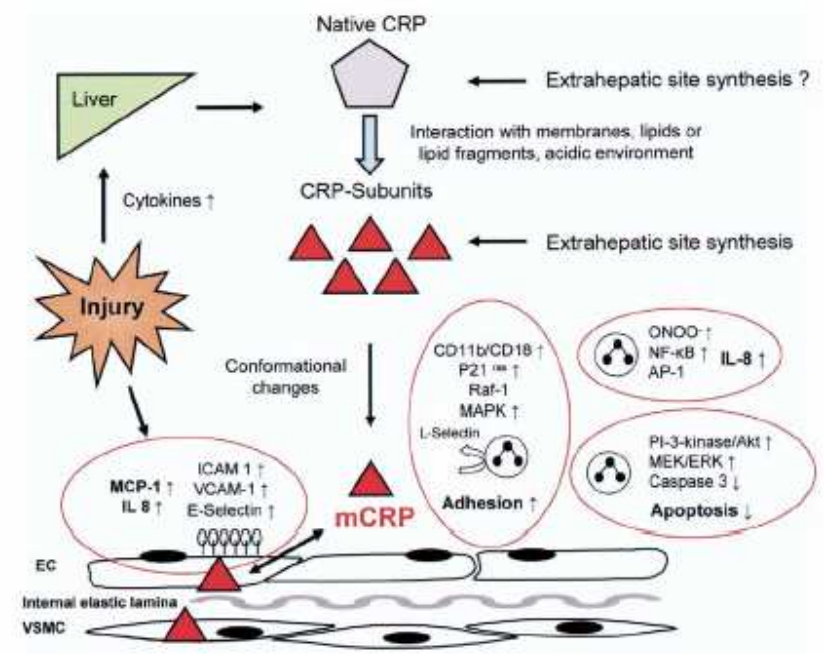

Fig 7. Illustration of the generation of mCRP and its potential mechanisms. mCRP. (adapted from 51)

2.4.3. Synthesis of CRP

The principal source of CRP production has been assumed to be the liver (19, 60). Serum CRP is synthesized by hepatocytes in the liver as a single-chain precursor with a cleavable signal sequence at the N terminus (13). CRP was initially thought to be produced and secreted only by hepatocytes under induction primarily by interleukin-6 (IL-6), with a synergistic effect of IL- 1 (13).

Recent data indicated that CRP was detected in arterial walls and that its expression was upregulated in atherosclerotic lesions, suggesting that vascular walls are one of the main CRP producers(19, 60). Adipose tissue acts as an important factor in modulating circulating hs-CRP levels (19, 60).

C-Reactive protein is the principal down-stream mediator of the acute phase response and is primarily derived via IL-6-dependent hepatic biosynthesis (53). IL-6 is largely responsible for the induction of CRP (16, 70) , although other cytokines such as IL-1 and transforming growth factor β(TGF-β) may also participate in this process (16, 51).

The efficiency of secretion of C-reactive protein, a process distinct from its synthesis, is greatly increased during the acute-phase response (51).

2.5. C-reactive protein (CRP) and Metabolic Syndrome

The metabolic syndrome is a constellation of abnormalities-generally considered to include abdominal obesity, high blood glucose/impaired glucose tolerance, dyslipidemia, and high blood pressure-that together increase risk of overt diabetes mellitus and cardiovascular disease (CVD). Each of the characteristics of metabolic syndrome is also independently associated with increased levels of CRP (68). The relationship of obesity to CRP as well as to other inflammatory markers, such as the proinflammatory cytokine interleukin-6(IL-6), has been the subject of intense scrutiny

(68).

In a study that examed CRP in healthy subjects, levels of CRP and IL-6 were found to be related to insulin resistance, blood pressure, HDL-C and endothelial dysfunction(68). These data support the concept that a low level of chronic inflammation may induce insulin resistance and endothelial dysfunction, which links them with obesity and CVD (68). Strong associations were identified between CRP levels and body mass index (BMI), waist circumference and fasting insulin-all of which are diagnostic criteria for metabolic syndrome (68). CRP was found to be a predictors, including baseline BMI, fasting triglycerides and serum glucose concentrations. In addition, there was a graded increase in risk over CRP quintiles, with a three-fold increase in risk between the lowest and highest quintiles at five years (68).

A variety of data indicate that glucose intolerance plays a central role in coronary artery disease (CAD) risk. Many recent findings indicating that elevated levels of inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), increase risk of diabetes and CVD, it has also been proposed that inflammation, as measured by such markers, be included in the definition of the syndrome (68). Elevated CRP added clinically significant prognostic information at all levels of severity of metabolic syndrome, with additive effects observed for those with four or five metabolic syndrome characteristics (all $P<0.001$) (68).

CRP levels and MetS have similar discriminatory power regarding subsequent

CVD risk has several possible interpretations. CRP could simply be acting as a marker for subclinical atherosclerosis "caused by" MetS variables.

Data from the National Health and Nutrition Examination Survey (NHANES) III have shown that obesity, insulin resistance, type 2 diabetes, and metabolic syndrome are associated with significantly elevated hsCRP levels (59).

2.6. C-reactive protein (CRP) and Cardiovascular Disease

Atherosclerosis is recognized as the pathological basis of cardiovascular disease (CVD) and recent advances in basic science have shown that it should be considered as a chronic inflammatory process (60). Evidence now indicates that inflammation contributes considerably to the initiation and progression of atherosclerosis, and histopathological and immunochemical observations suggest that active inflammatory processes may trigger plaque rupture and enhance the risk of coronary thrombosis leading to a clinical ischemic event (70). Inflammation is thought to play a key role in the progression of atherosclerosis. Some systemic inflammatory markers can indicate the severity of inflammation, and their levels have actually been associated with coronary disease (70). C-reactive protein (CRP) is an inflammatory marker that has been studied as a predictor of future coronary risk (67).

Both elements of the innate and the adaptive immunity appear to be actively involved in atherogenesis. In fact, the potential role played by pattern-recognition

receptors (Toll-like receptors and scavenger receptors), cytokines (such as IL-1, IL-6, TNF α), chemokines and pentraxines (such as CRP and PTX3) represents an emerging field of investigation in atherogenesis (60).

There are several plausible mechanisms by which CRP might increase the risk of an acute coronary event (71). CRP accumulates in macrophage-rich regions of developing atherosclerotic lesions. It can upregulate some macrophage proinflammatory cytokines and can induce tissue factor in monocytes (71). It can mediate uptake of native low-density lipoprotein (LDL) by macrophages, thereby potentially contributing to foam cell formation (71). It can induce adhesion molecule expression in endothelial cells (71), and plasma levels have been shown to correlate with impairment in endothelial vasoreactivity (71). CRP might be the link between chronic infection and coronary heart disease (CHD).

To date, several large, prospective epidemiological studies have consistently shown that CRP plasma level is a strong, independent predictor of risk of future CVD both in patients with previous cardiovascular events and healthy subjects. High levels of CRP are independent determinant of the risk of coronary heart disease, stroke, and peripheral arterial disease (60). The more obvious interpretation for the cardiovascular prognostic power of CRP is that this protein can be considered just as a sensitive marker of the inflammatory process that characterizes progression and complication of atherosclerosis (60).

CRP be used as a risk marker for cardiovascular disease in individual with a Framingham risk score of between 10 and 20%. In their recommendations, CRP levels of <1 mg/L were considered low-risk, 1-3 mg/L was average risk and >3 mg/L was high risk for cardiovascular disease (82). However, if the CRP level is >10 mg/L, then CRP cannot be used to assess cardiovascular risk and other active inflammatory processes (eg, trauma, infection, etc) should be excluded. Thus, when using CRP to assess cardiovascular risk in primary prevention, one needs to adopt the high sensitive (hs) CRP assay, and the patient should be free from any kind of acute inflammation such as infection, trauma, etc, for at least 2 weeks (86). Elevated risk of cardiovascular disease is typically observed among those with CRP values above 2 mg/L, but in some studies elevated risk is seen above 1 mg/L [29]. The relative risk for coronary heart disease to be 50% higher for those with CRP levels in the highest third of the respective study populations compared to those with levels in the lowest third [58].

Several cardiovascular disease risk factors are associated with higher CRP levels including, smoking, blood pressure, diabetes, body mass index, and abdominal adiposity [71-73]. CRP is associated with lower HDL cholesterol and higher triglyceride levels, but is, at best, only weakly associated with total and LDL cholesterol levels [70, 73]. CRP levels are lower in physically active older adults [29]. The pattern of association between CRP and alcohol consumption mirrors the relationship between alcohol consumption and vascular risk in that non-drinkers and heavy drinkers have

higher CRP levels than light-to-moderate drinkers [29].

C-reactive protein has traditionally been considered a nonspecific marker of the inflammatory process or an acute phase reactant (59, 75). While elevated levels of CRP are strongly associated with risk for disease, they do not infer disease; they infer the presence of an inflammatory state, regardless of whether they are a risk factor or risk marker for CVD (59). The strong epidemiologic associations between CRP and CVD outcomes are independent of other cardiovascular risk factors (59).

Prospective epidemiologic studies can provide further evidence on whether CRP is a risk factor for CHD. Nearly all reported prospective studies of CHD and CRP (71) have shown CRP to be positively associated with CHD incidence. A recent meta-analysis reported a pooled relative risk of 2.0 (95% CI 1.6-2.5) comparing the highest to lowest thirds of CRP in population-based studies (71). The ARIC study has already reported that most risk factors correlated with CRP were associated with incident CHD and carotid atherosclerosis (71).

Metabolic syndrome and CRP at baseline were independently related to risk of cardiovascular events, even after adjustments for age and sex (68). After adjustment for traditional risk factors, incident MI-coronary death, but not angina, was significantly associated with CRP, interleukin-6, and fibrinogen, but only interleukin-6 remained significantly associated with MI-coronary (70).

2.7. C-reactive protein(CRP) and Gender Influence

In a cross-sectional analysis, markers of inflammation, including CRP, were more strongly related to insulin resistance and/or the NCEP MetS in women than in men (32). Stronger relationships in women than in men between CRP levels and measures of insulin resistance and all the features of the MetS (32). CRP levels appear to increase modestly with age through middle age in men, but not in women [72, 73].

The gender differences observed are not explained by HRT use, but it is possible that endogenous estrogen is responsible. An alternative explanation is that in subjects with the metabolic syndrome, women might have greater quantities of total body adipose tissue compared with men, and this could be the source of proinflammatory cytokines (32).

Higher levels of CRP in women than in men but higher levels of insulin resistance in men than in women, suggesting that inflammation as assessed by CRP is not the main pathophysiological process leading to insulin resistance (32).

CRPtg mice revealed a sexually dimorphic pattern of expression, i.e., baseline and endotoxin-induced expression of human CRP in CRPtg males is significantly higher than the corresponding values females (52). This effect is due to testosterone, as baseline blood CRP in males is lowered following castration and because subsequent reconstitution with testosterone fully restores the ability of castrated males to express baseline blood CRP. Importantly, castration and testosterone replacement has no effect

on the level of CRP expressed during the endotoxin-induced acute phase response. This finding is likely relevant to humans, as at least one recent study shows that baseline blood CRP levels in men are significantly higher than in women (52).

3. SUBJECTS AND METHODS

3.1. SUBJECTS

Study participants (n=658) were all men in nondiabetic states [mean age: 48.3±0.44 yrs (21-70 yrs) and mean body mass index: 24.5±0.10 kg/m^2 (18.5-33.9 kg/m^2)]. Diabetes was ascertained according to the American Diabetes Association Criteria in which diabetes is defined as a fasting plasma glucose concentrations ≥ 7mmol/L (126mg/dl) or current treatment with antidiabetic agents. Subjects were recruited from responders to advertisements for a clinical nutrition study conducted by the Clinical Nutrition Research Lab and Cardiovascular Genome Center at Yonsei University. Subjects with orthopedic limitations, weight loss/gain over the previous 6 months or any diagnosis of cardiovascular, liver, renal, thyroid or pituitary disease were excluded. None of them were taking any medication. Written informed consent was obtained from all subjects and the protocol was approved by the Institute of Review Board of Yonsei University.

3.2. Materials and methods

3.2.1. Anthropometric and blood pressure measurements

Body weight and height were measured unclothed and without shoes in the morning. Body mass index (BMI) was calculated as body weight in kilograms divided by height in square meters (kg/m^2). Body fat percentages were measured with a TBF-105 body fat analyzer (Tanita Corp. Tokyo, Japan). Waist circumferences were measured with paper tape horizontally at the umbilicus in the standing position after normal expiration. Blood pressure was read from the left arm of seated patients with an automatic blood pressure monitor (TM-2654, A&D, Tokyo, Japan) after 20 minutes of rest. The average of three measurements was recorded for each subject.

3.2.2. Blood collection

Venous blood specimens were collected in EDTA-treated and plain tubes after a 12-hour fast. The tubes were placed on ice until they arrived at the laboratory room (within 1-3 hours) and were stored at -70°C until analysis.

3.2.3. Serum lipid profile

Concentrations of total cholesterol and triglyceride were measured using commercially-available kits and a Hitachi 7150 Autoanalyzer (Hitachi Ltd. Tokyo, Japan). After precipitation of serum chylomicrons, low density lipoprotein (LDL), and VLDL using dextran sulfate-magnesium, the high density lipoprotein (HDL) cholesterol left in the supernatant was measured using an enzymatic method. LDL cholesterol was estimated indirectly using the Friedewald formula for subjects with a serum triacylglycerol concentration <400mg/dL. Apolipoprotein AI and B were determined by turbidometry at 340nm using a specific anti-serum (Roche, Basel, Switzerland)

3.2.4. Fasting concentrations of glucose and insulin, and HOMA-IR

Fasting glucose was measured by glucose oxidase method using a Beckman Glucose Analyzer (Beckman Instruments, Irvine, CA, USA). Insulin was measured by radio-immunoassays with commercial kits from Immuno-Nucleo Corporation (Stillwater, MN, USA). Insulin resistance (IR) was calculated with homeostasis model assessment (HOMA) using the following equation: HOMA-IR={fasting insulin (μIU/ml)×fasting glucose (mmol/l)}/22.5.

3.2.5. Plasma adiponectin, C-reactive protein, fibrinogen and platelet count

Plasma adiponectins were measured by an enzyme immunoassay (Human Adiponectin ELISA kit, B-Bridge International Inc., Sunnyvale, CA, USA). The resultant color reaction was read using a Victor^2 (Perkin Elmer life sciences, Turka, Finland) at 450 nm. C-reactive proteins (CRP) were measured with an Express$^+$ autoanalyzer (Chiron Diagnostics Co., Walpole, MA, USA) using a commercially-available, high-sensitivity CRP-Latex (II) X2 kit (Seiken Laboratories Ltd., Tokyo, Japan). Fibrinogens were measured using a Stago compact (Diagnostic Stago, France) and the mass is calculated from a calibration curve and expressed as mg/dL. The numbers of platelet were measured by electric resistance method using an Automatic Blood Cell Counter (LC-240A, HORIBA Co., Japan)

3.2.6. Plasma LDL particle size and oxidized LDL

Particle size distribution of LDL (d1.019-1.063g/ml) isolated by sequential floatation ultracentrifugation was examined by a pore-gradient lipoprotein system (CBS Scientific, CA, USA) using commercially available non-denaturing polyacrylamide slab gels containing a linear gradient of 2-16% acrylamide (Alamo Gels

Inc., San Antonio, TX USA). Standards of latex beads (34nm), thyroglobulin (17nm), apoferritin (12.2nm) and catalase (10.4nm) were used to estimate the relative migration (Rf) rates of each band. The gels were scanned by GS-800 Calibrated Imaging Densitometer (Bio-Rad Laboratories, Graz, Austria). LDL particle size was calculated with reference to the Rf value of the standards. Plasma ox-LDL was measured using an enzyme immunoassay (Mercodia, Uppsala, Sweden). The resultant color reaction was read using a Victor^2 (Perkin Elmer life sciences, Turku, Finland) at 450nm. Quantification of ox-LDL was performed with using the peak area ratio and multiplied the sample dilution factor.

3.2.7. Statistical analysis

We used SPSS Window ver12.0 (Statistical Package for the Social Sciences, SPSS Ins., Chicago, IL, USA) for all analyses. We performed 'Pearson correlation' tests to observe the relationship between plasma adiponectin, CRP and other variables and 'stepwise multiple regression' analysis for finding major influencing factors on plasma adiponectin and CRP. We subdivided study subjects into 4 groups according to median concentrations of plasma adiponectin (4.3μg/mL) and CRP (0.36μg/mL); higher adiponectin-lower CRP (n=172), higher adiponectin-higher CRP (n=159), lower adiponectin-lower CRP (n=153), lower adiponectin-higher CRP (n=174). We performed

the analysis of covariance (ANOVA) and a general linear model (GLM) followed by Bonferroni method with adjustment for covariate if differences were shown in baseline clinical characteristics. The association between plasma adiponectin/CRP and metabolic syndrome was analyzed by χ^2 test and odds ratios (ORs) were calculated along with 95% confidence intervals (CIs) before and after adjusting for covariates. Before statistical tests, each variable was examined to ensure normal distribution; significantly skewed variables were log-transformed. For descriptive purposes, mean values are presented as untransformed and unadjusted. Results are expressed as mean±SE. A two-tailed value of $P<0.05$ was considered statistically significant.

4. RESULT

4.1. General characteristics of study subjects

Table 1 presents general characteristics of study subjects (n=658). Their mean values of age, BMI, waist circumference, body fat percent, systolic and diastolic blood pressures, plasma adiponectin and CRP were 48.3±0.44yrs, 24.5±0.10kg/m^2, 86.9±0.28cm, 22.6±0.20%, 125.2±0.64mmHg, 79.5±0.44mmHg, 0.93±0.06μg/mL, and 4.82±0.10μg/mL respectively. In addition, 38% of study subjects were current smokers, 28.4% were never smokers, and 33.6% were ex-smokers. In alcohol consumption, 78.2% were current drinkers, 20.0% were never-drinkers and 1.70% were ex-drinkers.

Table 1. General characteristics of study subjects

	Subjects (n=658)
Age (years)	48.3 ± 0.44
Body mass index (kg/m^2)	24.5 ± 0.10
Waist circumference (cm)	86.9 ± 0.28
Body fat (%)	22.6 ± 0.20
Systolic Blood pressure (mmHg)	125.2 ± 0.64
Diastolic Blood pressure (mmHg)	79.5 ± 0.44
Cigarette smoking (%)	
Never/Current/ex-smokers	28.4 / 38.0 / 33.6
Alcohol consumption (%)	
Never/Current/Ex-drinkers	20.0 / 78.2 / 1.70
Plasma adiponectin (μg/mL)	0.93 ± 0.06
Plasma C-reactive protein (μg/mL)	4.82 ± 0.10

Mean±S.E.

4.2. Pearson correlation between adiponectin, C-reactive protein and other variables

Table 2 shows the correlation between adiponecin, CRP and other variavbles. Plasma adiponectin and CRP were negatively correlated (r=-0.118, p=0.002).

Adiponectin had negative correlation with anthropometric parameters such as BMI (r=-0.209, p<0.001), waist circumference (r=-0.186, p<0.001) and %body fat (r=-0.162, p<0.001). In biochemical parameters, circulating adiponectins were inversely correlated with serum triglyceride (r=-0.283, p<0.001), atherogenic index (r=-0.230, p<0.001), apolipoprotein B (r=-0.170, p<0.001), fasting glucose (r=-0.207, p=0.001), insulin (r=-0.184, p<0.001), HOMA-IR (r=-0.220, p<0.001), oxidized LDL (r=-0.091, p=0.025) and platelets (r=-0.095, p=0.020) and positively correlated with HDL-cholesterol (r=0.259 p<0.001), apolipoprotein AI (r=0.139, p=0.001) and LDL particle size (r=0.258, p<0.001) (Table 2).

On the other hand, plasma CRP were positively correlated with age, (r=0.148, p<0.001), BMI (r=0.160, p<0.001), waist circumference (r=0.118, p=0.003), triglyceride (r=0.093, p=0.022), atherogenic index (r=0.091 p=0.021), fasting glucose (r=0.153, p<0.001), insulin (r=0.132, p=0.001), HOMA-IR (r=0.156, p=0.001), fibrinogen (r=0.260, p<0.001) and platelets (r=0.113, p=0.006) and negatively correlated with HDL cholesterol (r=-0.097, p=0.014), apolipoprotein AI (r=-0.008, p=0.021), and LDL particle

size (r=-0.100, p=0.012).

However, both adiponectin and CRP had no significant correlation with total cholesterol, LDL cholesterol and diastolic blood pressure.

Table 2. Pearson correlation between plasma concentrations of adiponectin, C-reactive protein and other variables in nondiabetic Korean men

	Adiponectin [Φ]	CRP [Φ]
	R	R
Adiponectin [Φ]	-	-0.118 **
C-reactive protein [Φ]	-0.118 **	-
Age (years)	0.003	0.148 ***
Body mass index	-0.209 ***	0.160 ***
Waist circumference	-0.186 ***	0.118 **
Body fat percent	-0.162 ***	0.076 §
Systolic blood pressure	-0.034	-0.113 **
Diastolic blood pressure	-0.050	0.021
Triglyceride [Φ]	-0.283 ***	0.093 *
Total cholesterol	-0.048	-0.013
HDL cholesterol	0.259 ***	-0.097 *
LDL cholesterol	-0.032	-0.023
Atherogenic index [1]	-0.230 ***	0.091 *
Apolipoprotein AI	0.139 **	-0.080 *
Apolipoprotein B	-0.170 ***	0.068
Fasting glucose	-0.207 **	0.153 ***
Fasting Insulin [Φ]	-0.184 ***	0.132 **
HOMA-IR[2] [Φ]	-0.220 ***	0.156 **
LDL particle size	0.248 ***	-0.100 *
Oxidized LDL	-0.091 *	-0.034
Fibrinogen	-0.052	0.260 ***
Platelet [Φ]	-0.095 *	0.113 **

[Φ] Log-transformed, § p<0.1, * p<0.05, ** p<0.01, *** p<0.001

[1]Atherogenic index = (total cholesterol-HDL cholesterol)/HDL cholesterol

[2] HOMA-IR = {fasting insulin (μIU/ml) x fasting glucose (mmol/l)}/22.5

4.3. Stepwise multiple regression analysis to identify major influencing factors on circulating adiponectin and C-reactive protein

To identify the major environmental factors influencing plasma adiponectin and CRP, we performed stepwise multiple analyses with adiponectin and CRP as dependent variables and age, BMI, waist circumference, % body fat, cigarette smoking and alcohol drinking as independent variables (Table 3). Regarding to circulating adiponectin, we found BMI was the first influencing factor (adjusted β-coefficient: -0.202, $p<0.001$, $R=0.202$, $p<0.001$). We also found that BMI was the first factor (adjusted β-coefficient: 0.203, $p<0.001$) and age was the second one (adjusted β-coefficient: -0.304 $p<0.001$) affecting CRP concentrations ($R=0.227$, $p<0.001$).

Table 3. Stepwise multiple regression analyses to identify major influencing factors on circulating adiponectin or C-reactive protein in nondiabetic Korean men

Dependent variable	Model	Independent Variable	Unstandardized		Adjusted	p-value	R	p-value
			β -coefficients	Constant	β-coefficients			
Adiponectin[Φ]	1	Body mass index	-0.048	2.58	-0.202	<0.001	0.202	<0.001
C-reactive protein[Φ]	1	Body mass index	0.100	-3.383	0.203	<0.001	0.227	<0.001
	2	Age	-0.030		-0.304	<0.001		

[Φ] LN, log transformed.

Included independent variables: age, body mass index, waist circumference, % body fat, cigarette smoking and alcohol drinking

4.4. According to median levels of circulating adiponectin and CRP: Lipid profiles, insulin resistance, LDL particle size and coagulation

To observe the patterns of lipid profile, insulin resistance and coagulation according to concentrations of plasma adiponectin and CRP, we subdivided study subjects into 4 groups according to median concentrations of plasma adiponectin (4.3μg/ml) and CRP (0.36μg/ml); higher adiponectin-lower CRP (>4.3μg/ml, ≤0.36μg/ml, n=172), higher adiponectin-higher CRP (>4.3μg/ml, >0.36μg/ml, n=159), lower adiponectin-lower CRP (≤4.3μg/ml, ≤0.36μg/ml, n=153) and lower adiponectin-higher CRP (≤4.3μg/ml, >0.36μg/ml, n=174). Mean age of 4 groups were 46.3±0.1.01, 50.4±0.77, 47.9±0.95 and 49.2±0.76 yrs (P=0.008) and mean BMIs were 23.6±0.19, 24.2±0.20, 24.4±0.19, and 25.7±0.21 kg/m^2 (P<0.001), respectively. As these mean values were significantly different among 4 groups as well as they turn out to be major influencing factor on adiponectin and CRP, we adjusted them when testing biochemical parameters.

In lipid profile, subjects with higher adiponectin had lower triglycerides (P0<0.001, P1<0.001, P2<0.001) and higher HDL cholesterol (P0<0.001, P1<0.001, P2<0.001) regardless of CRP concentrations before (P0) and after the adjustment (P1: adjusted for age and BMI, P2: adjusted for age, BMI, cigarette smoking and alcohol drinking) (Fig 8).

'higher adiponectin' groups also showed lower atherogenic index and lower apolipoprotein B as compared with 'lower adiponectin/higher CRP' group (P0<0.001, P1=0.004, P2=0.006) (Fig 9). Serum apolipotrotein-AI was significantly higher in higher adiponectin groups regardless of CRP concentrations (P0=0.017) but the significant turn to tendency after adjustment (p1=0.093, p2=0.072) (Fig 10).

Subjects with lower adiponectin/higher CRP showed significantly higher fasting glucose concentrations as compared with the other groups (P0<0.001, P1=0.005, P2=0.003) (Fig 11). This group also showed significantly highest fasting insulin (P0<0.001, P1=0.023, P2=0.016) (Fig 11), highest HOMA-IR (P0<0.001, P1=0.003, P2=0.002) and lowest LDL particle size (P0<0.001, P1<0.001, P2<0.001) among four groups (Fig 12). 'lower adiponectin but lower CRP' group also showed significant differences in these values in comparison of 'higher adiponectin/lower CRP' group (Fig 8-12). On the other hand, oxidized LDL tended toward higher in subjects with lower adiponectin (lower CRP: 56.9±2.26mg/dl, higher CRP: 59.1±1.67 mg/dl) than those with higher adiponectin (lower CRP: 54.1±1.80 mg/dl, higher CRP: 52.8±1.61 mg/dl), but it was not statistically significant (P0=0.057, P1=0.062, P2=0.066).

Platelet counts were higher in subjects with lower adiponectin/higher CRP than those with higher adiponectin/lower CRP (P0=0.037, P1=0.020, P2=0.034) (Fig 13). On the other hand, fibrinogen concentrations were higher in subjects with higher CRP concentration regardless of adiponectin concentration (P0=0.002) but the significant turn

to tendency after adjustment (P1=0.063, P2=0.057) (Fig 13). However we could not find any significant differences in total cholesterol (194.7±2.54, 197.8±2.75, 201.8±3.26, 198.8±2.52 mg/dl, p=0.337) and LDL cholesterol (118.6±0.96, 121.2±2.74, 123.3±3.07, 120.5±2.57mg/dl, p=0.656) among 4 groups.

In subjects with BMI≥24.5 (median value), we also observed the similar patterns like shown in figure 2. (data not shown).

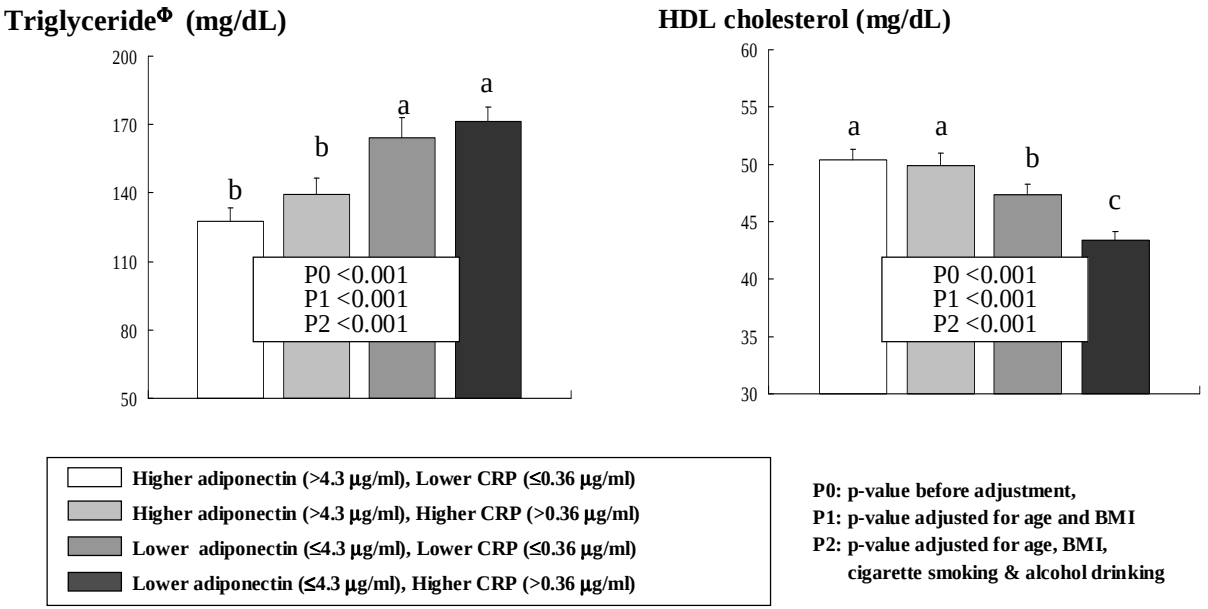

Figure 8. Biochemical parameters according to plasma adiponectin and CRP

Mean±S.E.

Different alphabet indicates significant difference ($p<0.05$) based on one-way ANOVA or general linear model followed by Bonferroni method after adjustment

Φtested after log transformed.

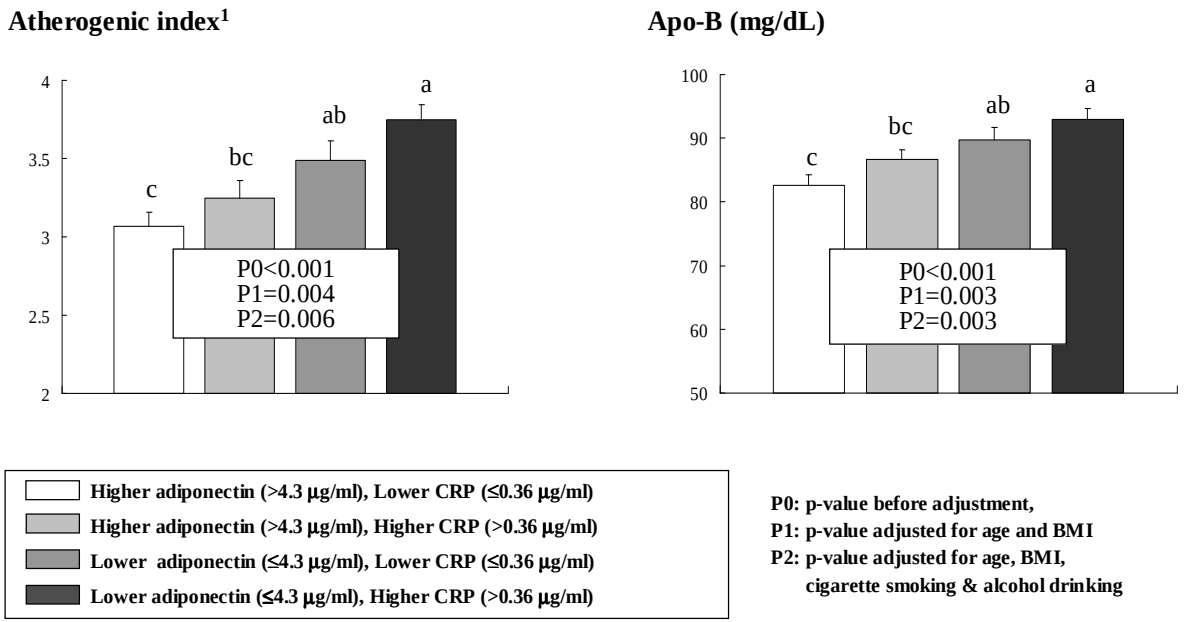

Figure 9. Biochemical parameters according to plasma adiponectin and CRP

Mean±S.E.

Different alphabet indicates significant difference ($p<0.05$) based on one-way ANOVA or general linear model followed by Bonferroni method after adjustment

[1]AI=(total cholesterol-HDL cholesterol)/HDL cholesterol.

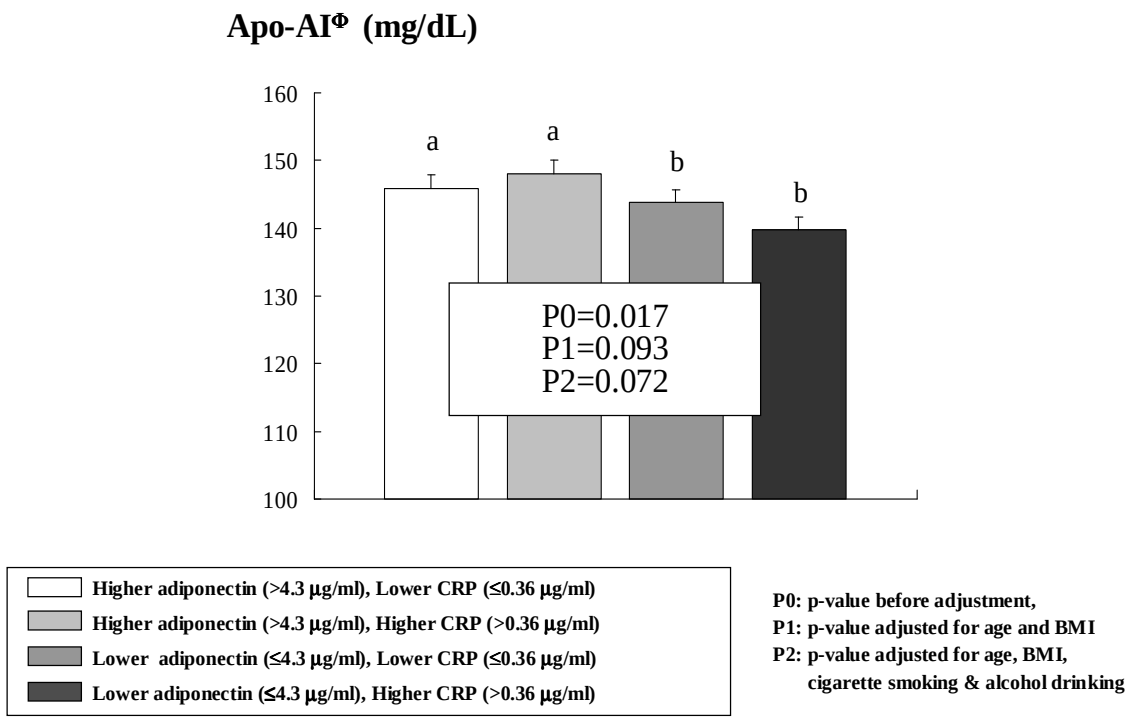

Figure 10. Biochemical parameters according to plasma adiponectin and CRP

Mean±S.E.

Different alphabet indicates significant difference ($p<0.05$) based on one-way ANOVA or general linear model followed by Bonferroni method after adjustment

Φtested after log transformed.

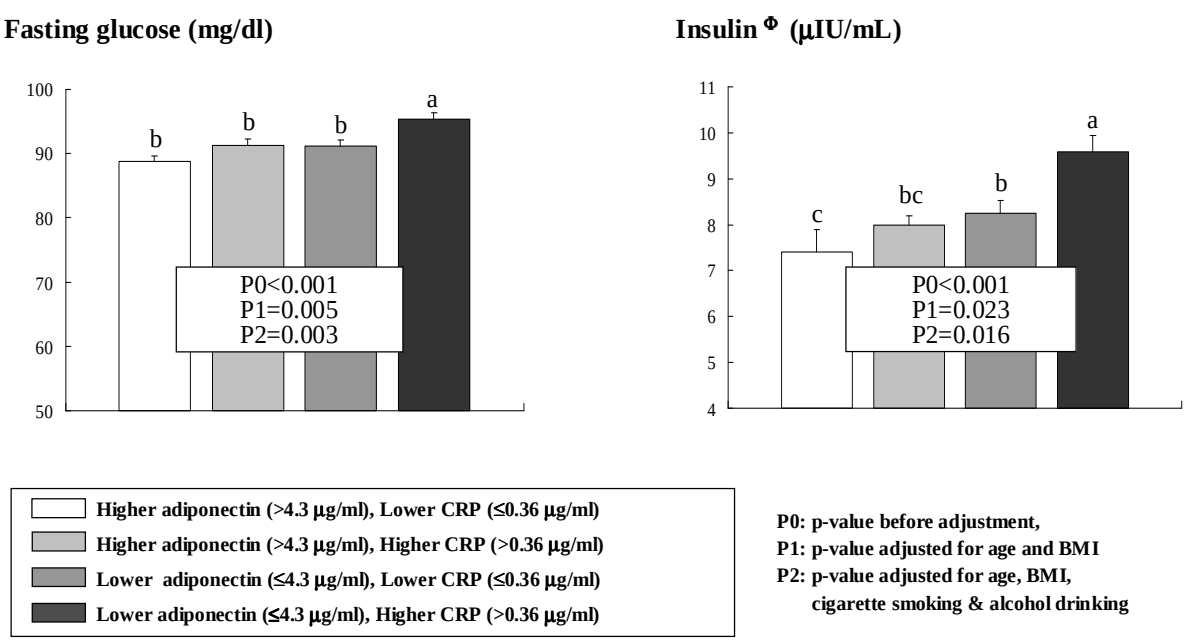

Figure 11. Biochemical parameters according to plasma adiponectin and CRP

Mean±S.E.

Different alphabet indicates significant difference ($p<0.05$) based on one-way ANOVA or general linear model followed by Bonferroni method after adjustment

Φtested after log transformed.

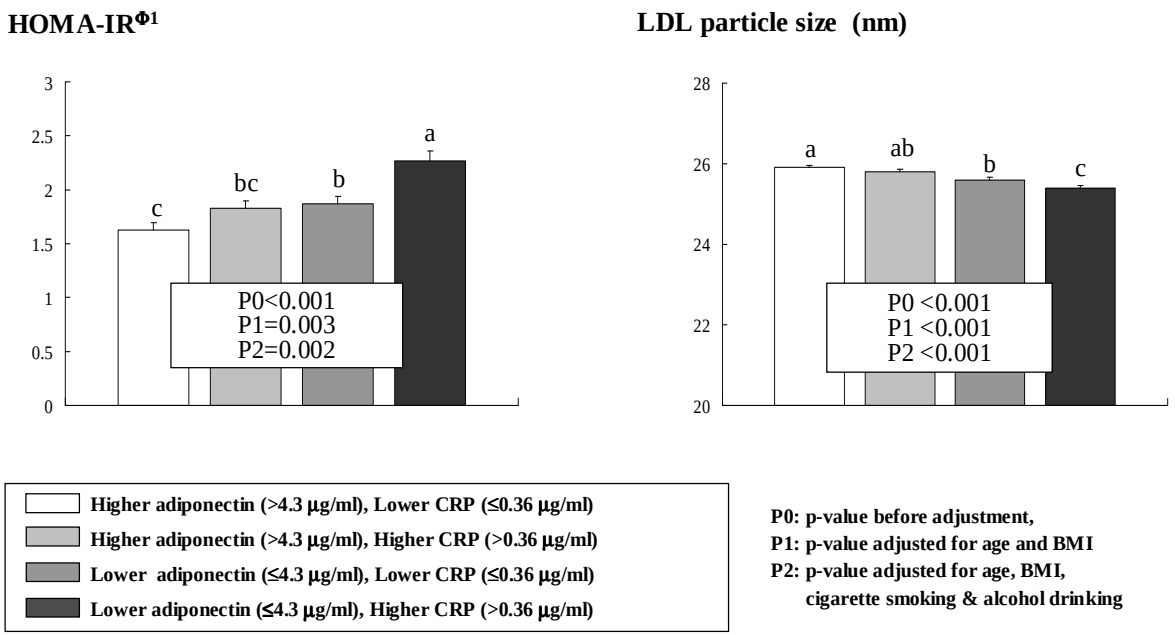

Figure 12. Biochemical parameters according to plasma adiponectin and CRP

Mean±S.E.

Different alphabet indicates significant difference ($p<0.05$) based on one-way ANOVA or general linear model followed by Bonferroni method after adjustment

Φtested after log transformed, [1]HOMA-IR={fasting insulin (μIU/ml) × fasting glucose (mmol/l)}/22.5

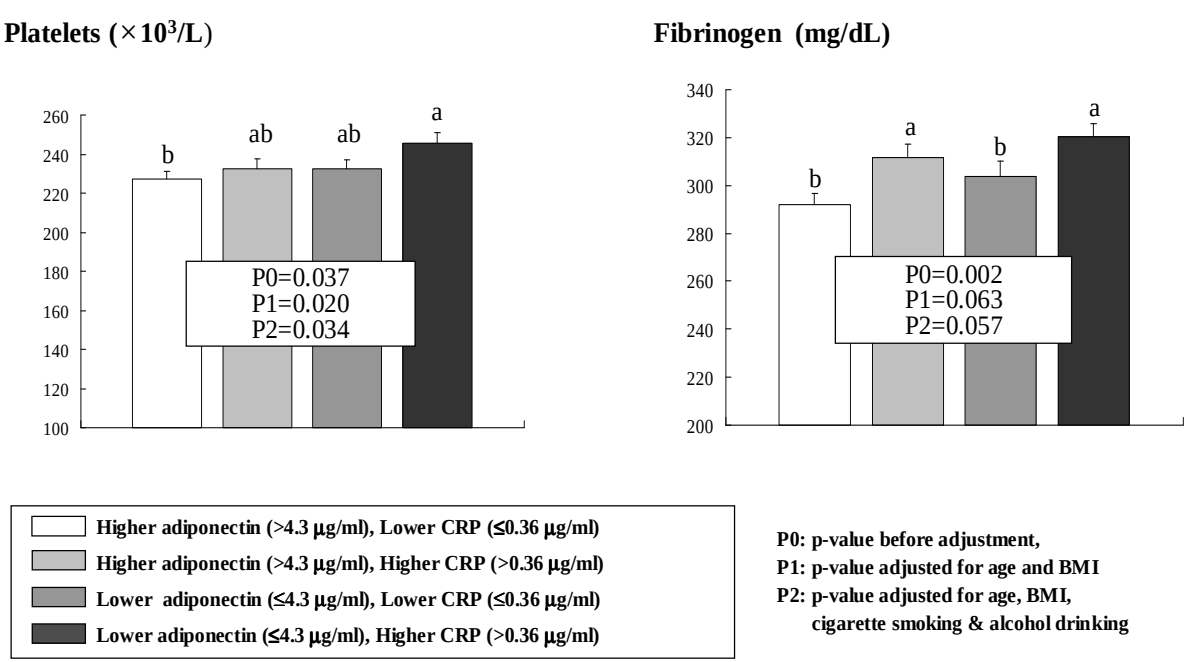

Figure 13. Biochemical parameters according to plasma adiponectin and CRP

Mean±S.E.

Different alphabet indicates significant difference ($p<0.05$) based on one-way ANOVA or general linear model followed by Bonferroni method after adjustment

4.5. Distribution and odd ratio on metabolic syndrome according to concentrations of adiponectin and CRP

We subdivided study subjects into those with or without metabolic syndrome (MetS). Definition of MetS was followed by NCEP ATPIII guideline with Asian-Pacific guideline. It included at least threes among waist circumference: >90cm, (Asian pacific guideline), triglyceride: ≥150mg/dl, HDL cholesterol: <40mg/dl, blood pressure: ≥130/≥85mmHg, or fasting glucose: ≥110mg/dl (28)

Proportion of MetS were 13.4% in 'higher adiponectin/lower CRP', 13.2% in 'higher adiponectin/higher CRP', 22.2% in 'lower adiponectin/lower CRP' and 31.5% in 'lower adiponectin/higher CRP' ($p<0.001$).

Compared with 'higher adiponectin/lower CRP' group, 'lower adiponectin/lower CRP group' and 'lower adiponectin/higher CRP group' had higher risk of MetS [OR1: 1.581, (CIs:1.035-3.331), P=0.038 OR1: 2.994, (CIs:1.739-5.154, P<0.001, respectively]. When adjusted for age, BMI, cigarette smoking and alcohol drinking, 'lower adiponectin /higher CRP group' still showed higher risk of MetS [OR2: 2.213, (CIs:1.123-4.362, P=0.022, OR3: 2.253, (CIs:1.085-4.677, P=0.029] (Table 4).

As compared with 'higher adiponectin/higher CRP' group, we also found that 'lower adiponectin/lower CRP' group and 'lower adiponectin/higher CRP group' had

higher risk of MetS [OR1: 1.878, (CIs:1.034-3.410), P=0.039, OR0: 3.037, (CIs:1.736-5.314, P<0.001, respectively. 'lower adiponectin/higher CRP group' still showed higher risk of MetS when adjusting for age and BMI, [OR2: 2.087, (CIs:1.173-3.714, P=0.012], but the significance disappeared when adjusted for age, BMI, cigarette smoking and alcohol drinking (Table 4).

Table 4. Odds ratio for metabolic syndrome among the concentrations of adiponectin and CRP*

Category	Comparison	OR1 (95% CI)	p	OR2 (95% CI)	p	OR3 (95% CI)	p
Higher adiponectin Lower CRP	Higher adiponectin/Higher CRP	0.986 (0.522-1.861)	0.965	0.794 (0.364-1.731)	0.561	1.103 (0.381-3.191)	0.857
	Lower adiponectin/Lower CRP	1.581 (1.035-3.331)	0.038	0.968 (0.464-2.019)	0.931	1.136 (0.467-2.762)	0.778
	Lower adiponectin/Higher CRP	2.994 (1.739-5.154)	<0.001	2.213 (1.123-4.362)	0.022	2.253 (1.085-4.677)	0.029
Higher adiponectin Higher CRP	Lower adiponectin/Lower CRP	1.878 (1.034-3.410)	0.039	1.307 (0.631-2.706)	0.471	1.244 (0.485-3.189)	0.650
	Lower adiponectin/Higher CRP	3.037 (1.736-5.314)	<0.001	2.087 (1.173-3.714)	0.012	1.770 (0.733-4.275)	0.205
Lower adiponectin Lower CRP	Lower adiponectin/Higher CRP	1.618 (0.984-2.660)	0.058	1.432 (0.765-2.678)	0.261	1.143 (0.479-2.728)	0.763

*: Proportions of metabolic syndrome according to concentrations of adiponectin and CRP : Higher adiponectin/Lower CRP (13.4%), Higher adiponectin /Higher CRP (13.2%), Lower adiponectin/Lower CRP (22.2%) ,Lower adiponectin/Higher CRP (31.5%)

OR : Odds ratio, CI: confidence interval,

OR1: Unadjusted OR, OR2: Adjusted for age and body mass index, OR3: Adjusted for age, body mass index, cigarette smoking and alcohol drinkin

5. DISCUSSION

This present study showed the associate effect of plasma adiponectin and CRP on metabolic disorder and also maintaining higher circulating adiponectin may lower the risk of metabolic disorder even though plasma CRP concentrations are relatively high.

As we expected, subjects having lower adiponectin/higher CRP as compared with those having higher adiponectin/lower CRP, showed more metabolic disorder-increasing results such as higher levels of atherogenic index, apolipoprotein B, fasting glucose, fasting insulin, HOMA-IR and platelets count, and lower LDL particle size. Furthermore, we observed 'lower adiponectin/higher CRP' group are exposed at 2~3 time significantly higher risk of MetS than 'higher adiponectin/lower CRP' group even after adjusting for age, BMI, cigarette smoking and alcohol drinking [OR1: 2.994, (CIs:1.739-5.154, P<0.001, OR2: 2.213, (CIs:1.123-4.362, P=0.022, OR3: 2.253, (CIs:1.085-4.677, P=0.029].

As previously reported (1-4,19-21,29), we observed inverse correlation between adiponectin and CRP as well as significant relationships between each of adiponectin or CRP and adiposity, lipid profile, insulin resistance, LDL particle size, or coagulation markers. Adiponectin may not only reduce triglyceride accumulation in skeletal muscle by enhancing fatty acid oxidation but also decrease triglyceride synthesis by reducing the supply of non-esterified fatty acids to the liver for gluconeogensis (30). Therefore, reduced triglyceride accumulation and synthesis may influence fasting insulin and

insulin resistance (31), but adiponectin itself may also sensitize insulin concentrations (2). Long-term treatment with adiponectin showed the improvement of insulin sensitivity with reduced storage of triglyceride in liver and muscle (31). CRP was also reported to be associated with MetS and CVD (3,9,10); Framingham Offspring study showed that CRP concentrations were significantly higher in individuals with MetS than those without MetS and strongly correlated with number of MetS components (32). Highest quartile of CRP concentration showed three times-higher risk of myocardiac infarction compared with lowest quartile (9,33).

We also observed that subjects with higher adiponectin even under higher plasma CRP maintained the lower values of serum triglyceride, atherogenic index, insulin and insulin resistance, and the higher values of LDL particle size and HDL cholesterol. These results may be due to adiponectins being exclusively expressed in adipose tissue and being abundant in human plasma and thereby higher adiponectin concentrations may relatively buffer the negative influence of higher CRP on metabolic parameter (11). Another possibility is the characteristics of study subjects. Most studies were performed in subject with relatively severe obesity, diabetes or CVD, but our subjects were in from normal BMI to slight obesity (18.5~33.9), and were not diagnosed as diseases such like diabetes or CVD.

From these results, we found the associate effect of plasma adiponectin and CRP on metabolic disorder but we also assumed that in non-severe obesity and non-diabetic

states, maintaining higher adiponectin concentrations may relatively reduce the risk of metabolic syndrome even though plasma CRP concentrations are high.

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국 문 요 약

비당뇨병인 한국인 남성에서 혈중 C-reactive protein과 adiponectin 농도가 대사증후군의 위험도에 미치는 영향

혈장 adiponectin과 C-reactive protein (CRP)는 비만, 당뇨병 또는 심혈관계질환과 같은 대사 이상 질환과 관련이 있다고 밝혀져 있다. 본 연구에서는 비당뇨병인 한국인 남성에서 혈장 adiponectin과 CRP의 대사 이상에 어떤 영향을 미치는지를 조사하였다.

비당뇨병인 한국남자(21-70세, 체질량지수: 18.5~33.9kg/m^2) 658명을 대상으로 하였고 대상자들을 adiponectin (4.36 μg/mL)과 CRP (0.36 μg/mL)의 중간 농도에 따라서 높은 adiponectin농도/낮은 CRP농도군 (172명), 높은 adiponectin농도/높은 CRP농도군 (159명), 낮은 adiponectin농도/낮은 CRP농도군 (153명), 낮은 adiponectin농도/높은 CRP농도군 (174명) 4그룹으로 나누었다. 본 논문에서는 인체계측 지표들, 지질 수준, 인슐린 저항성 정도, 혈장 adiponectin, 혈장 CRP, LDL particle size와 응고 지표들을 측정하였다.

혈장 CRP 농도와 상관없이 높은 adiponectin농도를 가진 군에서 낮은 adiponecin 농도를 가진 군에 비해서 나이, 체질량 지수, 흡연, 알코올 섭취를 보정

전(모든 P값 <0.001)과 보정 후(모든 p값 <0.01)에 낮은 혈청 중성지방, 낮은 atherogenic index, 낮은 인슐링 저항성, 높은 HDL 콜레스테롤과 높은 LDL particle size를 가지는 것으로 나타났다. 또한 4그룹 중에서 낮은 adiponectin농도/높은 CRP농도를 가진 군은 보정 전과 보정 후에 가장 높은 공복 혈당, 높은 인슐린 저항성, 높은 platelets 그리고 가장 낮은 LDL particle size(p<0.001)를 가질 뿐만 아니라 높은 adiponectin농도/낮은 CRP농도를 가진 군과 비교해서 보정 전 [OR:2.994 (CIs:1.739-5.154) p<0.001]과 보정 후 [OR:2.253 (CIs:1.085-4.677) p=0.029]에 대사 증후군에 더 높은 위험도를 가지는 것으로 나타났다.

이러한 결과를 바탕으로, 심하지 않은 비만과 비당뇨병 상태에서 혈장 adiponectin과 CRP가 대사 이상에 영향을 미치는 것을 알 수 있고, 혈장 CRP농도가 높더라도 높은 adiponectin 농도를 유지하는 것이 대사 증후군의 위험도를 상대적으로 낮출 수 있을 것이라는 것을 알 수 있다.

핵심되는 말: adiponectin, C-reactive protein, 비당뇨병의, 대사증후군