疑義解釈資料の送付について（その1）

平成24年3月30日

「診療報酬の算定方法の一部を改正する件」（平成24年厚生労働省告示第76号）等については，「診療報酬の算定方法の一部改正に伴う実施上の留意事項について」（平成24年3月5日保医発0305第1号）等により，平成24年4月1日より実施することとしているところであるが，今般，その取扱いに係る疑義照会資料を別添1から別添5のとおり取りまとめたので，参考までに送付いたします

なお，改定説明会等にて回答した事項についても，本事務連絡を確認の上，適切に運用頂くようお願いします．

【リハビリテーション】

（問152）リハビリテーションの初期加算について，リハビリテーション科を標榜している必要があるか．

（答）原則として標榜している必要がある．ただし，リハビリテーションに専ら従事している常勤の医師が勤務している場合は，リハビリテーション科を標榜していない場合であっても，当該加算を算定出来る

また，心大血管疾患リハビリテーションについては，当該リハビリテーションの経験を有する常勤の医師が勤務している循環器科又は心臓血管外科，呼吸器リハビリテーションについては，呼吸器リハビリテーションの経験を有する常勤の医師が勤務している呼吸器内科，呼吸器外科を標榜していることで差し支えない．

解　説

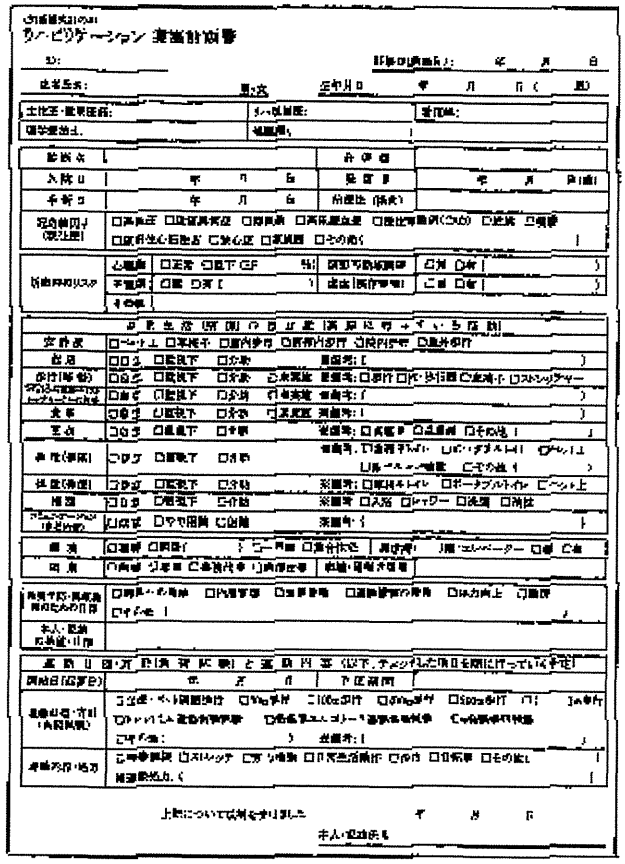
① 「リハビリテーション科」の標榜は原則としては必要．

② ただし，リハビリテーションに専従している常勤医師が勤務していればリハビリテーション科の標榜は必ずしも必要ない．

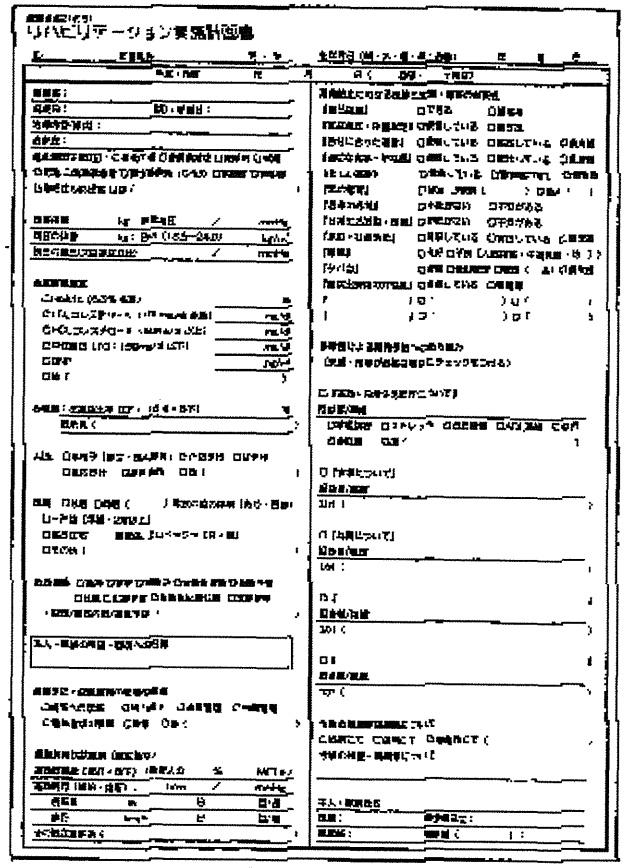
③ 「心大血管疾患リハビリテーション」については，「心リハの経験を有する常勤医が勤務している循環器科又は心臓外科を標榜していればよい」ということなので，心大血管疾患リハの施設基準を満たしていれば問題ない．

変更点2

リハビリテーション実施計画書およびリハビリテーション総合実施計画書の従来の様式に加えて，心大血管疾患リハビリテーション用に合わせた「リハビリテーション実施計画書（別紙様式21の4）（入院用），（別紙様式21の5）（外来用）」「リハビリテーション総合実施計画書（別紙様式23の4）」が新たに掲載されました．本学会が見本を作成して要求してきた様式が厚生労働省に正式に採用されたわけです．



別紙様式21の4



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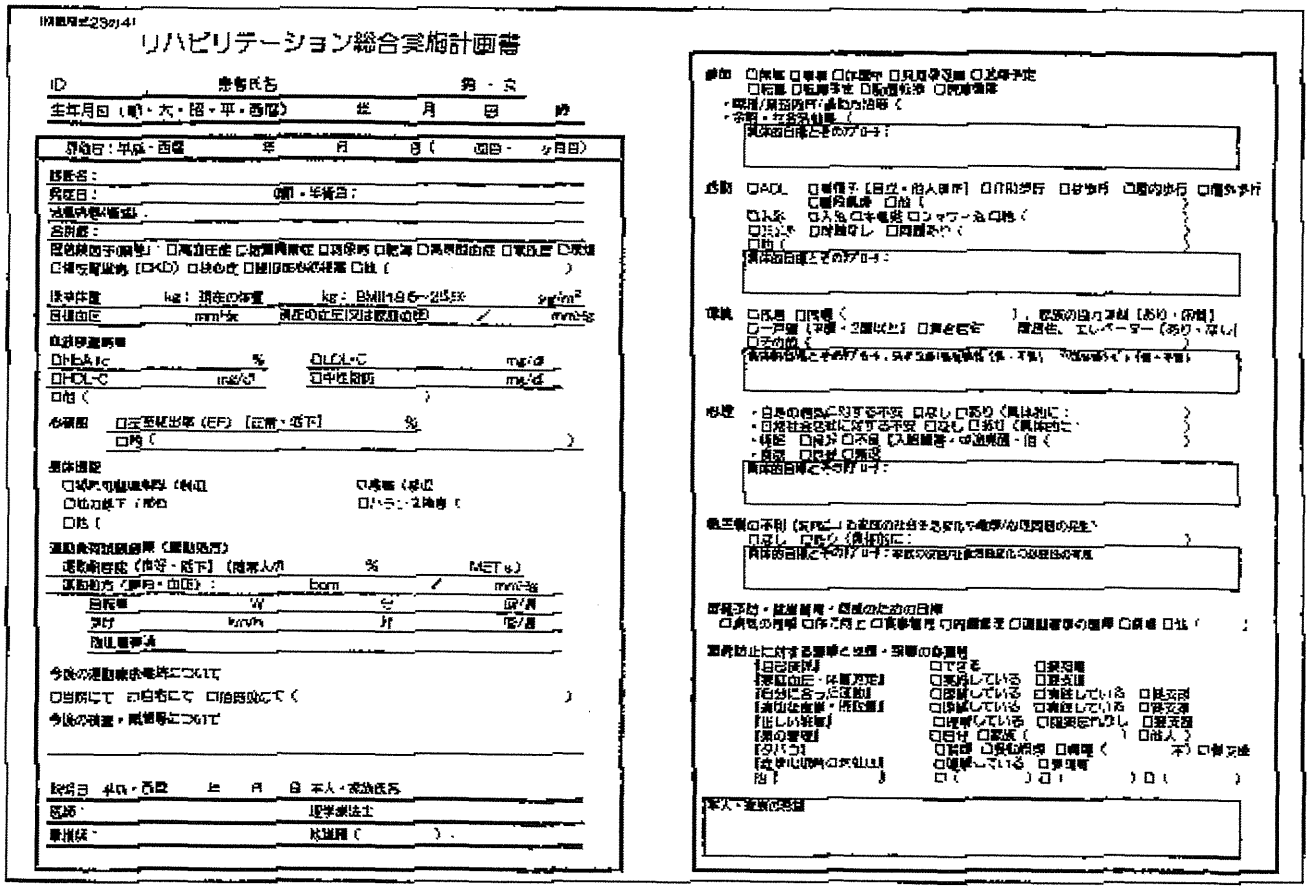

別紙様式23の4

REVIEW ARTICLE

A Paradigm Shift in Rehabilitation Medicine: From "Adding Life to Years" to "Adding Life to Years and Years to Life"

Masahiro KOHZUKI[1] , Yoshiko SAKATA[1] , Takayuki KAWAMURA[2]
Satoru EBIHARA[1] , Osamu ITO[1]

1) Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Japan
2) Department of Health Service Management, Tohoku Fukushi University, Japan

Address for Correspondence:
Masahiro Kohzuki M.D., Ph. D.,
Professor and Chairman
Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai 980-8574 Japan.
Tel +81-22-717-7353
FAX +81-22-717-7355
e-mail: kohzuki@med.tohoku.ac.jp

ABSTRACT

Medical science basically aims to "Adding Years to Life" by increasing life expectancy. Rehabilitation aims to "Adding Life to Years" by helping patients with impairment achieve, and use, their full physical, mental and social potential. However, recent growing evidence suggests that rehabilitation for patients with visceral impairment such as cardiac, renal and pulmonary impairment can not only improve exercise performance and quality of life, but also increases survival. Therefore, modern comprehensive rehabilitation for patients with visceral impairment does not simply aim to "Adding Life to Years" but "Adding Life to Years and Years to Life" which is a new rehabilitation concept. Moreover, comprehensive cardiac rehabilitation is feasible and effective for secondary prevention after transient ischemic attack or mild, non-disabling stroke, offering a promising model for vascular protection across chronic disease entities. Therefore, modern comprehensive rehabilitation should improve not only quality of life but also biological lifespan in patients with impairment. This modern comprehensive rehabilitation is an ideal modern medicine and urgent efforts should be made urgently to increase the implementation rate of the rehabilitation.

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"Adding Years to Life" and "Adding Life to Years"

The goal of rehabilitation is to ensure the best possible physical, psychological and social conditions for patients with chronic or post-acute cardiac disease so that they may, by their own efforts, preserve or resume their proper place in the society 1).

There is a word "Adding Years to Life". This means that medical science basically aims to improve biological lifespan. In contrast, there is a word "Adding Life to Years" which means that improvement quality of life in the life.

Rehabilitation aims to "Adding Life to Years" by helping patients with impairment achieve, and use, their full physical, mental and social potential.

Recent evidence suggests that rehabilitation increases survival

However, recent growing evidence suggests that rehabilitation including exercise training for patients with visceral impairment can not only improve exercise performance and quality of life, but also increases survival.

For example, the American Heart Association (AHA) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) define cardiac rehabilitation (CR) programs as, "Coordinated, multifaceted interventions designed to optimize a cardiac patient's physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of the underlying atherosclerotic processes, thereby reducing morbidity and mortality" 1). CR is an integral component of the continuum of care for patients with cardiovascular diseases and recent studies have indicated that CR not only alleviates symptoms, but also improves QOL and increases survival in patients with acute myocardial infarction (AMI) 1). Moreover, a growing evidence base suggests that exercise training in patients with stable CHF can reduce exertional symptoms and improve exercise performance and quality of life without adversely affecting left ventricular geometry or contractility 1). Recent studies have indicated that exercise training not only alleviates symptoms, but also improves vascular function and produces positive effects on heart function and increases survival in patients with congestive heart failure (CHF) 2). There has recently been a paradigm shift in the management of CHF.

Moreover, levels of physical exercise among chronic kidney disease (CKD) patients with hemodialysis are low. Increased physical activity in this population has been associated with improved ability and capacity to perform activities in everyday life, occupational tasks, health-related QOL and survival. Therefore renal rehabilitation including regular exercise is recommended to this population and produces positive effects on ADL and QOL with increasing survival in CKD patients with hemodialysis 3). We have established the Japanese Association of Renal Rehabilitation in 2011 to evaluate and promote renal rehabilitation (3, 4).

Chronic obstructive pulmonary disease (COPD) by smoking is a worldwide public health problem. Many patients with COPD lead unsatisfying, sedentary existences, worn down

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by years of dyspnea and exacerbations. A downward spiral links progressive inactivity to accelerating disability and premature mortality. Indeed, cross-sectional COPD studies have demonstrated that inactivity is a potent predictor of early death. A physiological variable — the forced expiratory volume in one second (FEV_1) — is often used to grade the severity of COPD. However, patients with COPD have systemic manifestations that are not reflected by the FEV_1. Celli et al. 5) established the BODE index (the body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E), measured by the six-minute–walk test), a simple multidimensional grading system, is better than the FEV_1 at predicting the risk of death from any cause and from respiratory causes among patients with COPD. Pulmonary rehabilitation significantly improved the quality of life and exercise tolerance without any change in the pulmonary function in patients with moderate COPD, and there was also a large decrease in the risk of death in rehabilitated patients as measured using the BODE index 6).

"Adding Life to Years and Years to Life"

Therefore, modern comprehensive rehabilitation for patients with visceral impairment such as cardiac, renal and pulmonary impairment does not simply aim to "Adding Life to Years" but "Adding Life to Years and Years to Life" which is a new rehabilitation concept.

Moreover, comprehensive cardiac rehabilitation is feasible and effective for secondary prevention after transient ischemic attack or mild, non-disabling stroke, offering a promising model for vascular protection across chronic disease entities. Therefore, modern comprehensive rehabilitation should improve not only quality of life but also biological lifespan in patients with impairment.

Low implementation rate of rehabilitation

The problem of rehabilitation for patients with visceral impairment is a low implementation. Because the beneficial effects of rehabilitation on exercise capacity, quality of life, and prognosis (mortality) in patients with visceral impairment have been established, the low implementation rate of rehabilitation implies that patients are kept away from the established benefits of rehabilitation by reasons unrelated to the patient conditions. Thus, efforts should be made urgently to increase the implementation rate of rehabilitation.

The CR program usually consists of three stages: the acute stage (phase I), subacute stage (stage II) and maintenance stage (phase III). Phase III CR is recognized as a community or home-based program committed to encourage exercise and a healthful lifestyle with the goal of minimizing the risk of recurring cardiac problems (secondary prevention). A recent study 7) demonstrated that the participation rate of recovery phase II CR to be 12% in the Japanese Circulation Society (JCS)-authorized cardiology-training hospitals (TH) and 5% in all the hospitals in Japan. Major reasons for not implementing CR were lack of staff, equipment and space, and the absence of the approval for the CR facility standards 7). However, THs are usually large-sized, general hospitals

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which would be expected to have sufficient staff, equipment, and space. In addition, 73% of THs that had been approved for specific intensive care did not have an approval for CR despite their ability to fulfill the CR facility standards indicates that there should be reasons other than the CR facility standards for the non-implementation of CR in these hospitals 7).

Ades et al 8) reported that by multivariate analysis, the strength of the physician's recommendation for participation was the most powerful predictor of cardiac rehabilitation entry in patients after AMI or coronary bypass surgery. Thus, physicians' reluctance or lack of proper understanding to use CR after AMI might be the reason for the low implementation rate of CR in Japan. Since the CR facility standards in Japan has been loosened in 2004 ,2006 and 2010, the motivation of physicians and hospitals would be a critically important factor for the implementation of CR.

CR as a success model of rehabilitation

The CR program usually consists of three stages: the acute stage (phase I), subacute stage (stage II) and maintenance stage (phase III). For the patients' benefit, phase III CR programs should be convenient, affordable, safe and enjoyable 9). The European Society of Cardiology also recommends that cardiac patients should be oriented to a long-term maintenance regimen with the use of support systems such as coronary clubs, gymnasiums or other facilities to promote long-term prevention strategies in the community. In Germany, a close network of currently approximately 6600 heart groups has been established 10), the concept of cardiac reconditioning centers for the prevention and rehabilitation of coronary patients has been tremendously successful 11).

Japan Heart Club and the certification program for the masters of CR

With support of the Japanese Association of Cardiac Rehabilitation (JACR), the Japan Heart Club (JHC), a non-profit organization, was established in 2004. The missions of JHC are to 1) organize scientific meetings and workshops for health promotion and prevention of cardiovascular diseases (CVD), 2) publish journals and learning materials for health promotion and prevention of CVD, 3) conduct research for health promotion and prevention of CVD, 4) organize facilities and develop programs for primary and secondary CVD prevention, 5) offer certification and education programs for the Master of Cardiac Rehabilitation (MCR), and other health-related professionals, 6) collaborate with national and international research institutes 9).

Certification program for MCR started in 2000. The objectives of the certification program are to improve quality of cardiac rehabilitation services and to educate the professionals playing a pivotal role in a primary CVD prevention programs in Japan. The JACR certifies those who understand the purpose of CR and have knowledge, skills and abilities for providing comprehensive CR program through a comprehensive team approach. Referring to American College of Sports Medicine certification objectives 12), the MCR certification examination is based upon the knowledge, skills and abilities (KSA's) in each of the 11 categories below 9).

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1. Anatomy and Biomechanics (4 KSAs)
2. Exercise Physiology (8 KSAs)
3. Electrocardiology (7 KSAs)
4. Human behavior and psychology (6 KSAs)
5. Pathophysiology (13 KSAs)
6. Clinical diagnosis and treatment (7 KSAs)
7. Health appraisal and fitness testing (10 KSAs)
8. Cardiac rehabilitation (3 KSAs)
9. Secondary prevention and patient education for CAD (11 KSAs)
10. Exercise programing (14 KSAs)
11. Safety, injury prevention and emergency care (3 KSAs)

Minimum requirements for candidates are as follows:

- Candidates must possess any of the following certifications or degrees: physician, registered nurse, physical therapist, occupational therapist, clinical laboratory technician, medical engineer, clinical psychologist, and/or exercise trainer.
- Have been a member of the JACR for more than 2 years.
- Have a minimum of 1 year of experience in a CR program or equivalent, and submit 10 case reports about the diagnosis, tests, treatment, and rehabilitation for patients with CVD.

The number of MCR has increased to 2336 by 2011. The MCR attracts health-related professionals with various backgrounds some of which include physical therapists, physicians, nurses, and clinical laboratory technicians.

Community-based Phase III CR & primary prevention programs in Japan

One of the missions for JHC is providing opportunities to participate in a CR program in the community. MedEX club, a multidisciplinary facility provides MCR-supervised exercise sessions, education for patients and training classes for citizens and health professionals. There are seven MedEx club regional branches and 11 classes are being offered nationwide.

The purpose of the MedEx club is to promote regular physical activity in CR patients and prevent cardiac disease and the recurrence of coronary events. Exercise training classes are held in various settings, some of which include hospitals, community centers, fitness facilities, and schools. The classes are typically held once or twice a week under the supervision of the MCRs 9). In the MedEx branch in Sendai, each session lasts 70 minutes and has a capacity of 12 people. Prior to and post-exercise session, participants measure their blood pressure and body weight and fill in the self-health check sheet. The exercise session starts with a 15 minute warm-up, either sitting or standing, followed by 15 minutes of aerobic exercise and 15 minutes of resistance training using elastic bands or their own body weight. The intensity of the aerobic exercise is determined by the cardiopulmonary exercise test measured upon entry to the club. Each session ends with cool down for 15 minutes which includes stretching of the major muscle groups. In addition to weekly exercise

sessions, each patient keeps a log for blood pressure and body weight in the morning and night as well as step counts and exercise energy expenditure measured by an accelerometer. The log is submitted to the MCR program every 2 weeks. The MedEx club mainly offers exercise-based CR program, but patients also learn about physical activity, lifestyle modification, psychological management from the MCRs and other participants 9).

Cardiac rehabilitation is an integral component of the continuum of care for patients with CVD, the MedEx club can offer convenient, affordable, safe and enjoyable phase III programs and, in the near future, it may be recognized as. a standard model of phase III CR service in Japan.

Conclusions

Comprehensive rehabilitation brings a paradigm shift from "Adding Life to Years" to "Adding Life to Years and Years to Life" in our modern rehabilitation world. This modern comprehensive rehabilitation is an ideal modern medicine and urgent efforts should be made urgently to increase the implementation rate of the rehabilitation.

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Adiponectin Pathway Attenuates Malignant Mesothelioma Cell Growth

Kaijun Niu[1,2,3], Masanori Asada[3], Tatsuma Okazaki[3], Shinsuke Yamanda[3], Takae Ebihara[3], Hui Guo[2], Dongying Zhang[2], Ryoichi Nagatomi[2], Hiroyuki Arai[3], Masahiro Kohzuki[1], and Satoru Ebihara[1]

[1]Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, [2]Division of Biomedical Engineering for Health and Welfare, Tohoku University Graduate School of Biomedical Engineering, and [3]Department of Geriatrics and Gerontology, Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Japan

Malignant mesothelioma (MM) is caused by exposure to asbestos. Because MM has a latency period, short survival time, and has a poor response to current therapeutic regimes, long-term preventive strategies are required to suppress the advance of pathological states after asbestos exposure. Accumulating evidence suggests that adiponectin plays a crucial role in the regulation of energy metabolism by increasing AMP-activated protein kinase (AMPK) activation. Several studies have indicated that the activation of AMPK decreases cyclooxygenase (COX)-2 expression. Because high COX-2 levels correlated with a worse prognosis and survival rate in MM, we examined whether the adiponectin pathway suppresses MM cell growth through the AMPK/COX-2 pathway. *In vivo*, dietary fish oil (a potential promoter of adiponectin) decreased the growth rate of MM, which was accompanied by an increase in adiponectin and phospho-AMPK levels, and a decrease in COX-2 level. *In vitro*, adiponectin significantly impaired the cell proliferation rate of MM cell lines. These effects partly involved induction of growth arrest and apoptosis to MM cells. MM cells expressed both adiponectin receptors 1 and 2 (AdipoR1 and -R2) at mRNA and proteins levels. These receptors were functional, because adiponectin activated AMPK. Adiponectin treatment also significantly down-regulated protein levels of COX-2 and its downstream prostaglandin E_2. Finally, inhibitory analysis of AdipoR1/R2 by small interfering RNA knockdown suggests that adiponectin enhances AMPK activity and impairs the cell proliferation rate of MM cells, mainly via AdipoR1. These findings suggest that the induction or supplementation of adiponectin is an important tactic for developing therapeutic strategies against MM.

Keywords: adiponectin; malignant mesothelioma; AMP-activated protein kinase; cyclooxygenase-2; fish oils

Malignant mesothelioma (MM) is a fatal cancer of increasing incidence associated with asbestos exposure (1). MM responds poorly to surgery, chemotherapy, and radiotherapy, and also has an appalling prognosis (2, 3). Although MM has a latency period of 15–40 years (4), the average survival time is generally accepted as 4–12 months (5). Therefore, long-term preventive strategies, including various lifestyle factors, are needed to suppress the advance of pathological states after asbestos exposure.

Fish oils rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are thought to suppress the pathogenesis of several human diseases, including cancer (6). Fish oils also increased adiponectin concentration in mice (7, 8). Several studies have reported that adiponectin inhibited carcinogenesis in a variety of experimental models (9–12). However, the precise mechanism of the anticarcinogenic effect of adiponectin has not been identified. Accumulating evidence suggests that adiponectin mediates the regulation of energy metabolism by increasing AMP-activated protein kinase (AMPK) activation (13). As a metabolic sensing signal, AMPK is involved in cancer cell apoptosis (14). A previous study suggested that AMPK played a critical role in cyclooxygenase (COX)-2 regulation (15). The apoptosis induced by high-dose H_2O_2 correlated with the activation of AMPK, and negatively correlated with COX-2 expression in human colon cancer cells (16). Moreover, other studies have suggested that AMPK activation decreased a COX-2 level in tumor cells (17, 18).

On the other hand, COX-2 overexpression has been noted in many solid tumors, including MM (19). High COX-2 levels in tumor sections correlated with a worse prognosis and survival rate of MM (20). Thus, we hypothesized that adiponectin might impair MM growth through the AMPK/COX-2 pathway. However, to the best of our knowledge, no previous studies have tested this issue. In this study, we examined the effect of dietary fish oils, which are potential promoters of adiponectin, on the growth of MM *in vivo* in association with adiponectin concentration and AMPK/COX-2 proteins in tumor tissues. We also examined the ability of adiponectin to impair MM cell growth through the modulation of AMPK/COX-2 signaling pathway *in vitro*. We observed that, *in vivo*, a fish oil diet decreased the growth rate of MM, which was accompanied by an increase in adiponectin and phospho-AMPK levels and a decrease in a COX-2 level in the tumors. *In vitro*, AMPK activation by adiponectin impaired COX-2 production in MM cells.

MATERIALS AND METHODS

Cells Culture

Four kinds of human MM site (pleural effusion)–derived cell lines, NCI-H2052, NCI-H28, NCI-H2452, and MSTO-211H, were obtained from the American Type Culture Collection (Manassas, VA). The MM cells were maintained in RPMI-1640 medium with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM Hepes, and 1.0 mM sodium pyruvate (American Type Culture Collection) supplemented with 10% FBS (MP Biomedicals, Morgan Irvine, CA), 100 U/ml penicillin, and 100 μg/ml streptomycin (Sigma, St. Louis, MO) in an incubator at 5% CO_2 at 37°C. The cells were split when subconfluent using trypsin/EDTA (Sigma) every 2–3 days. A human A673 rhabdomyosarcoma cell line was obtained from the European Collection of Cell Cultures (Salisbury, UK). This cell line was maintained in Dulbecco's modified Eagle medium (Gibco, Paisley, UK) supplemented with 10% FBS, 100 U/ml penicillin, and 100 μg/ml streptomycin.

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Correspondence and requests for reprints should be addressed to Satoru Ebihara, M.D., Ph.D., Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sebihara@med.tohoku.ac.jp

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

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Diets

The 20% (wt/wt) corn oil and menhaden fish oil (10–15% EPA and 8–15% DHA) diets were manufactured by Oriental Yeast Co., Ltd. (Chiba, Japan), and were sorted at 4°C and sealed in plastic bags *in vacuo*. A base diet was composed of 20% milk casein, 0.3% cystine, 14.2% α-starch, 10% sucrose, 23.8% cellulose, 1% vitamins, 3.5% mineral mixture, 0.25% choline bitartrate, and 0.5% tert-Butylhydroquinone.

In Vivo Tumor Models and Dietary Treatment

Male C.B-17/Icr-*scid* Jcl (*scid/scid*) (SCID) mice (6 wk old) were obtained from Clear Japan (Tokyo, Japan) and maintained under specific pathogen-free conditions throughout the study. Experiments were performed in accordance with the guidelines established by the Tohoku University Committee on Animal Research. SCID mice were placed on the usual mouse diet for 1 week, and then divided into two groups, each comprised of five animals: one group had unrestricted access to a corn oil diet, whereas the other group had unrestricted access to a menhaden fish oil diet. After 1 week, MSTO-211H cells (3×10^6 cells per animal) were injected subcutaneously into the hind flank of SCID mice, and the mice continued on the diets described previously here. Tumor size was quantified daily as width^2 × length × 0.52. Mice were killed on Day 25.

The Detection of Adiponectin Receptors 1 and 2 by Flow Cytometry

The cells were washed twice with PBS, trypsinized, and rewashed with 10 ml PBS. After washing, the cells were suspended with PBS supplemented with 2% FBS. Then, the cells were incubated on ice with a control rabbit IgG (Santa Cruz Biotechnology, Santa Cruz, CA), rabbit anti-adiponectin receptors (AdipoR) 1 and 2 antibody, followed by incubation with Alexa Fluor 488–conjugated goat anti-rabbit IgG (Invitrogen, Eugene, OR). Flow cytometry was performed with a FACSCalibur, and the data were analyzed with CellQuest software (BD Bioscience, San Jose, CA). Dead cells were excluded by propidium iodide staining.

Statistical Analysis

Data are presented as mean values (±SD). Differences were analyzed by one-way ANOVA (*post hoc*, Tukey). A Pearson's correlation coefficient (R) was calculated to evaluate the relationship between two continuous variables. The coefficient of determination was calculated by squaring the R. A level of P less than 0.05 was accepted as statistically significant. All experiments were repeated at least three times.

RESULTS

Effect of Fish Oil Diet on MM Growth and Its Possible Mechanism

To examine the effect of fish oil diet on the growth rate of MM *in vivo*, MSTO-211H cells were inoculated subcutaneously into SCID mice. There were no significant differences in amount of food intake (corn oil, 4.6 ± 0.1 g/mouse/d; fish oil, 4.5 ± 0.2 g/mouse/d) and animal weight gain (corn oil, +8.2 ± 1.3 g/25 d; fish oil, +7.8 ± 0.8 g/25 d) between the experimental groups. The tumor growth rate (Figure 1A) and tumor weight (Figure 1B, after 25 d) significantly decreased in the fish oil diet group relative to those in the corn oil diet group. Furthermore, fish oil diet increased serum adiponectin concentration (Figure 1C). The R^2 value showed that the serum adiponectin concentration was strongly related to tumor weight (Figure 1D; $R^2 = 0.76$, $P = 0.001$). We also examined the effect of corn oil or fish oil diet on protein levels of tumor adiponectin, phospho-AMPK, which suggests activation of AMPK, and COX-2. The tumor adiponectin and phospho-AMPK protein levels were 180 and 160% greater in the fish oil group than in the corn oil group, respectively. In contrast, the tumor COX-2 protein level was 30% lower in the fish oil group than in the corn oil group (Figure 1E). To determine the effect of the fish oil diet, we examined cell proliferation rate and number of apoptotic cells in tumor samples. Cell proliferation rate was analyzed by immunohistochemistry for Ki67 (Figure 1F). The rate of Ki67-positive cells significantly decreased in the fish oil diet group relative to the corn oil diet group, suggesting decreased cell proliferation rate in the fish oil diet group (Figure 1F, *graph*). To analyze further the effects of a fish oil diet on tumor growth, cell apoptosis was analyzed by terminal deoxynucleotidyl transferase dUTP nick end labeling assay on tumor samples (Figure 1G). The rate of terminal deoxynucleotidyl transferase dUTP nick end labeling–positive cells was greater in the fish oil diet group than in the corn oil diet group, suggesting an increase in the number of apoptotic cells in the fish oil diet group (Figure 1G, *graph*). Immunohistochemical staining showed that AdipoR1/R2 was recognized in the cell cytoplasm as well as in the cell membrane of MM cells (Figure 1H). Collectively, these experiments suggest that the fish oil diet decreases tumor growth rate by decreasing the cell proliferation rate and increasing the number of apoptotic cells, possibly through increasing an adiponectin level and decreasing a COX-2 level.

Adiponectin Impaired MM Cell Proliferation Rate

We examined the effect of adiponectin on the cell proliferation rate of MM cell lines, NCI-H2452, NCI-H28, NCI-H2052, and MSTO-211H. Treatment with adiponectin for 24 hours significantly impaired the cell proliferation rate of all of the cell lines in a dose-dependent manner (Figure 2A, *left four panels*). Similar to adiponectin, the impairment of cell proliferation rate was also observed in NCI-H2452 cells treated with 100 μM Meloxicam and NS-398, which are inhibitors of COX-2 (Figure 2A). Similar results were observed in three other kinds of MM cells (data not shown).

To examine the mechanisms of the inhibitory effects of adiponectin on cell proliferation rate, we examined the apoptotic index by annexin V–propidium iodide staining using flow cytometry (Figures 2B and 2C). The addition of adiponectin (10 μg/ml) or NS-398 (100 μM) to NCI-H2452 and MSTO-211H cells for 24 hours significantly increased the annexin V^+ population compared with the controls. In addition, DNA synthesis in cells was evaluated by measuring bromodeoxyuridine (BrdU) incorporation by flow cytometry. The addition of adiponectin (10 μg/ml) or NS-398 (100 μM) to NCI-H2452 and MSTO-211H for 24 hours significantly decreased the level of BrdU incorporation, which suggests a decrease in cell proliferation rate (Figures 2D and 2E). Similar results were observed in two other kinds of MM cells. Furthermore, the effect of adiponectin on activation of caspase-3, which is the central player in most apoptotic pathways, in MM cells was examined. We treated MM cells with adiponectin (10 μg/ml, 24 h) and immunohistochemically stained for activated caspase-3 (red), β-actin (green), and the nucleus (4′,6-diamidino-2-phenylindole; blue). Activated caspase-3 was detected in adiponectin-treated MM cells, but not in control MM cells (Figure 2F). Therefore, when taken together, our data suggest that adiponectin impairs the proliferation rate of MM cells, possibly through decrease in proliferation rate and the induction of cell apoptosis.

Expression of Adiponectin Receptors in MM Cells

AdipoR1 and -R2 are receptors of adiponectin *in vitro* and *in vivo* (13). AdipoR1/R2 mRNA and protein expression was determined by RT-PCR assay and Western blotting analysis in MM cells. RT-PCR showed bands specific to the AdipoR1 and -R2, respectively, suggesting expression of AdipoR1/R2 mRNAs in NCI-H2052, NCI-H28, NCI-H2452, and MSTO-211H cells, similar to

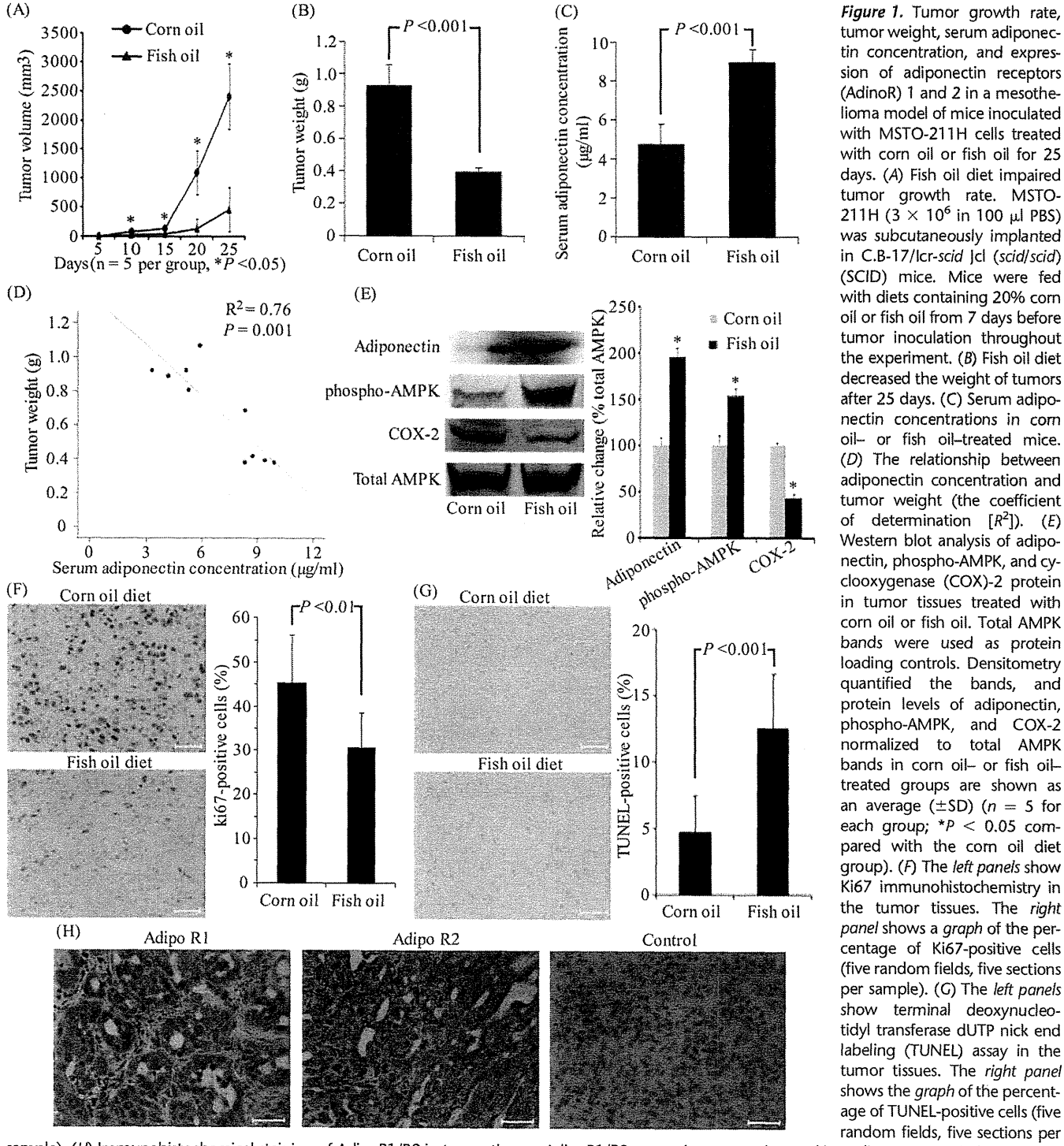

Figure 1. Tumor growth rate, tumor weight, serum adiponectin concentration, and expression of adiponectin receptors (AdinoR) 1 and 2 in a mesothelioma model of mice inoculated with MSTO-211H cells treated with corn oil or fish oil for 25 days. (*A*) Fish oil diet impaired tumor growth rate. MSTO-211H (3×10^6 in 100 μl PBS) was subcutaneously implanted in C.B-17/Icr-*scid* Jcl (*scid/scid*) (SCID) mice. Mice were fed with diets containing 20% corn oil or fish oil from 7 days before tumor inoculation throughout the experiment. (*B*) Fish oil diet decreased the weight of tumors after 25 days. (C) Serum adiponectin concentrations in corn oil– or fish oil–treated mice. (*D*) The relationship between adiponectin concentration and tumor weight (the coefficient of determination [R^2]). (*E*) Western blot analysis of adiponectin, phospho-AMPK, and cyclooxygenase (COX)-2 protein in tumor tissues treated with corn oil or fish oil. Total AMPK bands were used as protein loading controls. Densitometry quantified the bands, and protein levels of adiponectin, phospho-AMPK, and COX-2 normalized to total AMPK bands in corn oil– or fish oil–treated groups are shown as an average (±SD) (n = 5 for each group; *P < 0.05 compared with the corn oil diet group). (*F*) The *left panels* show Ki67 immunohistochemistry in the tumor tissues. The *right panel* shows a *graph* of the percentage of Ki67-positive cells (five random fields, five sections per sample). (*G*) The *left panels* show terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay in the tumor tissues. The *right panel* shows the *graph* of the percentage of TUNEL-positive cells (five random fields, five sections per sample). (*H*) Immunohistochemical staining of AdipoR1/R2 in tumor tissues. AdipoR1/R2 expressions were observed in malignant mesothelioma (MM) cells. Control staining is a negative control stained without the specific antibody. *Scale bars*, 50 μm.

positive control A673 cells (Figure 3A). Western blot analysis showed an expression of AdipoR1/R2 in NCI-H2052, NCI-H28, NCI-H2452, and MSTO-211H cells at the protein level, similar to positive control A673 cells (Figure 3B). Flow cytometric analysis showed an expression of AdipoR1/R2 in NCI-H2452 and MSTO-211H cells (Figure 3C). Similar expressions of AdipoR1/R2 were also observed in two other kinds of MM cells by flow cytometric analysis.

Adiponectin Decreased the Basal COX-2 Expression Level in MM Cells

Real-time RT-PCR showed a decreased expression level of the *COX-2* mRNA in the adiponectin-treated NCI-H2452 and MSTO-211H cells compared with controls (Figure 4A). To examine the effect of adiponectin on COX-2 protein production in NCI-H2452 and MSTO-211H cells, we treated the cells with adiponectin and immunohistochemically stained for COX-2

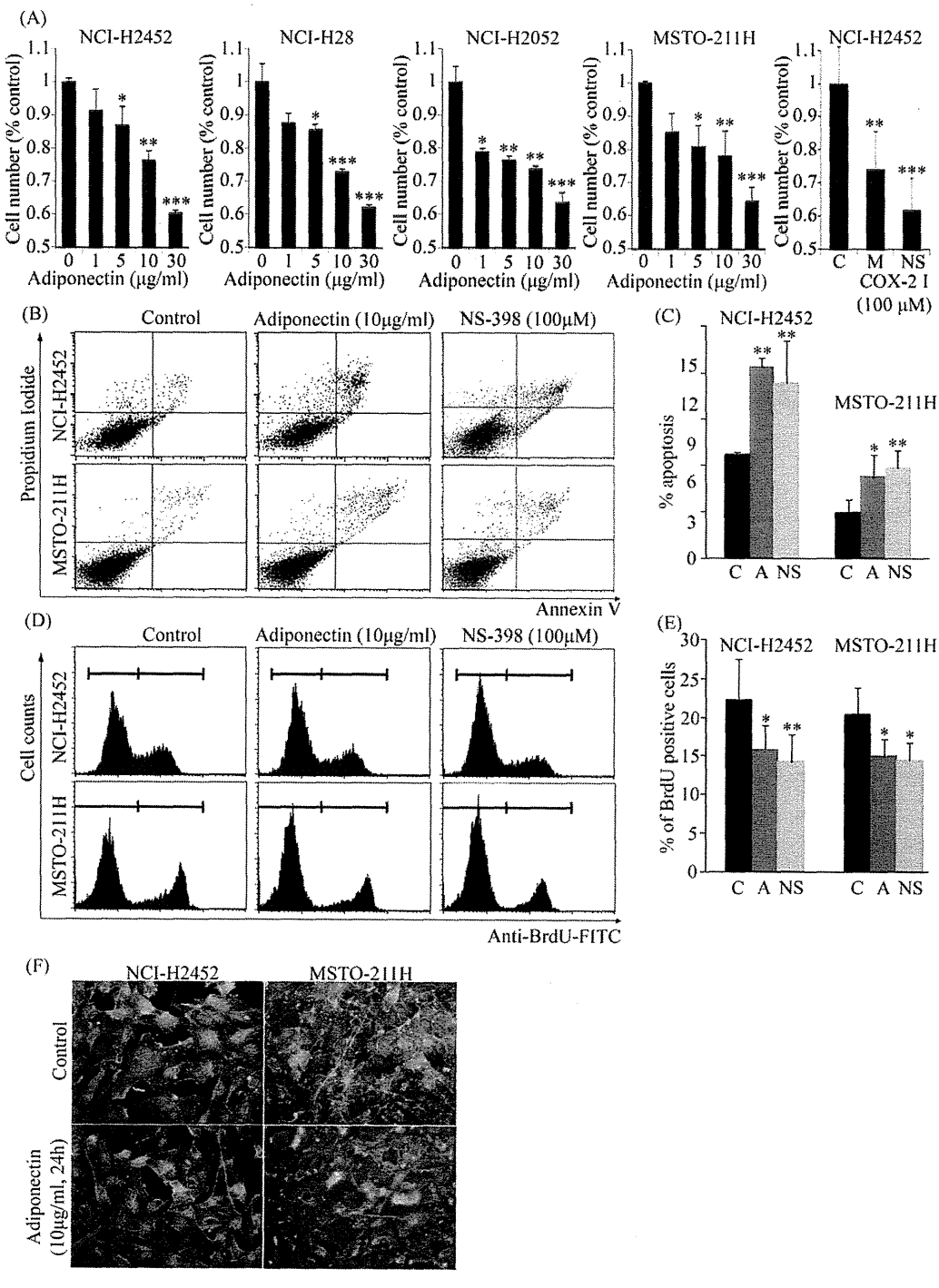

Figure 2. Adiponectin impairs MM cell growth. (*A*) The MM cells were treated with indicated concentrations of adiponectin, Meloxicam (M), or NS-398 (NS) for 24 hours (C, control). Cell proliferation rate was measured by a water-soluble tetrazolium (WST) assay. (*B*) NCI-H2452 and MSTO-211H cells were cultured with or without 10 μg/ml adiponectin or NS-398 for 24 hours, and were then double stained by Annexin-V (*x axis*) and propidium iodide (*y axis*). The representative FACS profile is shown. (*C*) NCI-H2452 and MSTO-211H cells were cultured for 24 hours with or without 10 μg/ml adiponectin, or NS-398, for 24 hours. Annexin-V–positive percentages were calculated as apoptotic cells. (*D*) Bromodeoxyuridine (BrdU) incorporation was evaluated by flow cytometry after stimulating the cells with control vehicle or 10 μg/ml adiponectin, or NS-398, for 24 hours. Representative data are shown. (*E*) NCI-H2452 and MSTO-211H cells were cultured for 24 hours with or without 10 μg/ml adiponectin, or NS-398, for 24 hours, and BrdU-positive percentages were calculated. (*F*) Immunocytochemistry was performed using anti–activated caspase-3 antibody (*red*), anti–β-actin antibody (*green*), and 4′,6-diamidino-2-phenylindole (DAPI), which stains for the nucleus (*blue*) (magnitude × 400). *Columns* indicate the mean of three different experiments performed in triplicate; *error bars*, SD. The significance of differences was calculated by ANOVA (*post hoc*, Tukey's method). $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ compared with the intact cells of each cell line. A, adiponectin; C, control; NS, NS-398.

(green) and β-actin (red). Adiponectin decreased the intensity of intracytoplasmic staining of COX-2 in NCI-H2452 cells and MSTO-211H cells (Figure 4B). Next, we employed ELISA to examine the effect of adiponectin on COX-2 protein level in NCI-H2452 and MSTO-211H cells. The protein level of COX-2 was significantly decreased in the adiponectin-treated group compared with the control group (Figure 4C). Because COX-2 metabolizes arachidonic acid released from the plasma membrane to generate prostaglandin E_2 (PGE_2), and PGE_2 in turn mediates many of the biological effects of COX-2, we also examined the effect of adiponectin on PGE_2 production in NCI-H2452 and MSTO-211H cells. PGE_2 concentrations in the culture supernatants were evaluated by ELISA. PGE_2 level was significantly decreased by adiponectin treatment (Figure 4D). Similar results were observed in two other kinds of MM cells (data not shown).

Modulation of AMPK Signaling Pathway by Adiponectin

Because previous studies have shown that the AMPK signaling pathway is involved in the regulation of COX-2 expression in colon cancer cells (15, 16, 18, 21), we examined the hypothesis that AMPK plays an important role in the regulation of COX-2 expression in MM cells (Figure 5). The adiponectin and 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR, a pharmacological activator of AMPK and its upstream AMPK

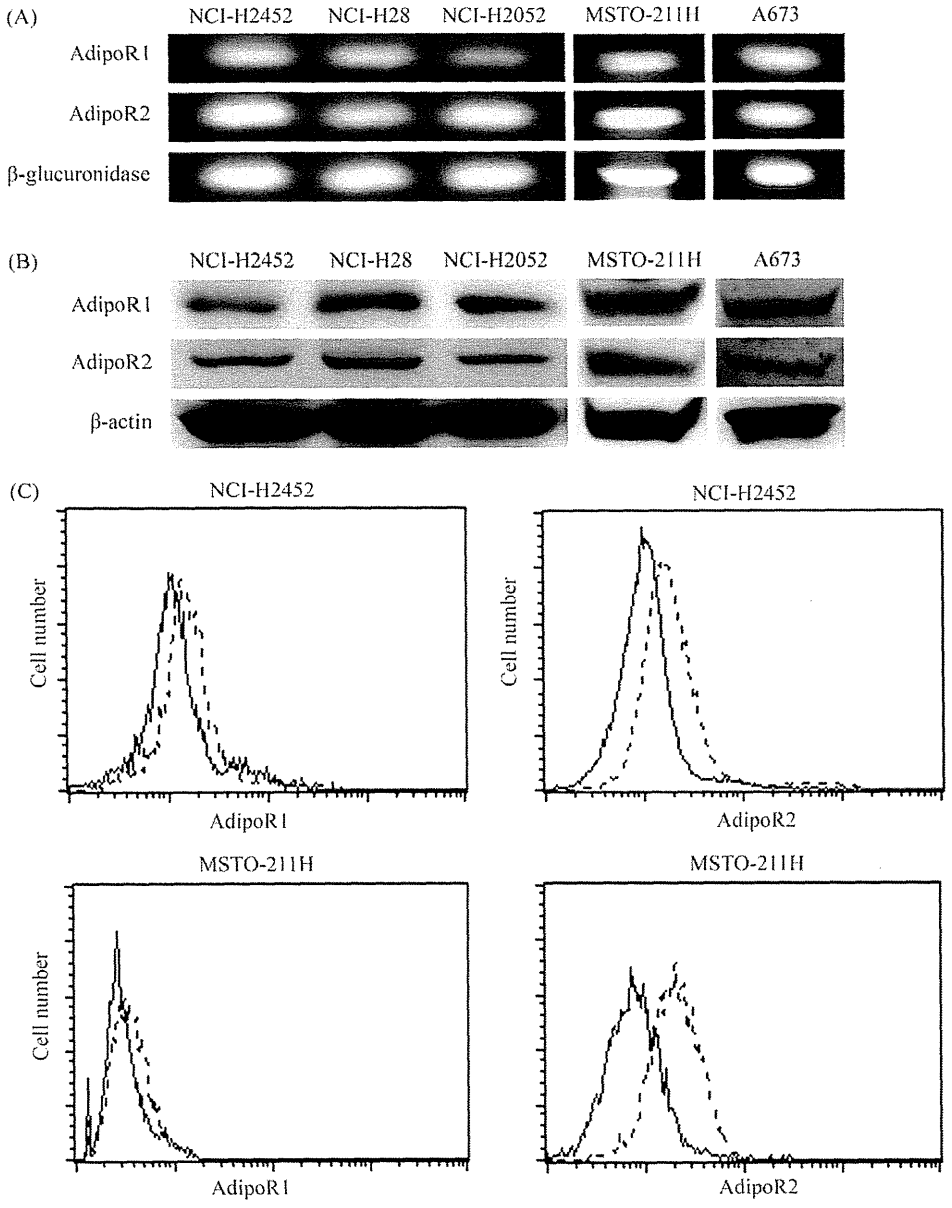

Figure 3. (*A*) AdipoR1/R2 mRNA expression in MM and A673 cells (a human rhabdomyosarcoma cell line) were used as a positive control. Total RNA was extracted from MM cells and analyzed by RT-PCR with the specific primers. PCR products were separated by 2% agarose gel electrophoresis. This figure shows one RT-PCR representative of three separate experiments. (*B*) AdipoR1/R2 protein levels in MM cells (A673 cells were used as a positive control). Cell lysates (100 μg) were subjected to Western blot analysis using anti-AdipoR1 or anti-AdipoR2 antibodies, as described in MATERIALS AND METHODS. (*C*) Flow cytometric analysis showed the specific expression of AdipoR1/R2 in NCI-H2452 and MSTO-211H cells. The *solid line* shows the staining with Alexa Fluor 488–conjugated control rabbit IgG. The *dashed line* shows the staining with Alexa Fluor 488–conjugated anti-AdipoR1/R2 antibody. Shown is one experiment representative of three.

kinase [AMPKK]) treatment increased a phospho-AMPK level and decreased a COX-2 level in NCI-H2452 and MSTO-211H cells (Figure 5A). In contrast, compound C, which is a cell-permeable, potent, selective, reversible, and ATP-competitive inhibitor of AMPK, prevented the effect of adiponectin on phospho-AMPK and COX-2 levels (Figure 5A). Similar results were observed in two other kinds of MM cells (data not shown).

We next examined the inhibitory effect of adiponectin in MM cells in which AdipoR1/R2 was specifically down-regulated by small interfering RNA (siRNA). The addition of siRNA, which targeted AdipoR1/R2, strongly suppressed the mRNA expression levels of corresponding receptors after 24- or 48-hour treatment, as evaluated by RT-PCR (Figure 5B) and Western blot analysis (Figure 5C). The siRNA of AdipoR1/R2 did not cross-react to each other's receptors. It is confirmed by RT-PCR and Western blot analysis (data not shown). The inhibition of AdipoR1 strongly abolished the adiponectin-induced decrease in COX-2 level and increase in the phospho-AMPK level. In contrast, inhibition of AdipoR2 did not abolish the adiponectin-induced decrease in the COX-2 level or increase in the phospho-AMPK level (Figure 5D). Similar results were observed in two other kinds of MM cells (data not shown).

Impairment of Cell Proliferation Rate Was Dependent on AdipoR1/R2

Finally, we examined the effect of adiponectin on impairment of the cell proliferation rate in MM cells in which AdipoR1 or -R2 were specifically down-regulated by siRNA. Down-regulation of AdipoR1 significantly restored the impairment of the cell proliferation rate by adiponectin (Figure 6). In NCI-H2452 and MSTO-211H cells treated with control siRNA, 10 μg/ml adiponectin impaired the cell proliferation rate by 15%, whereas the effect was significantly restored by AdipoR1 siRNA treatment (Figure 6). The adiponectin-induced cell proliferation rate impairment was not restored by AdipoR2 siRNA.

DISCUSSION

In this study, we found that *in vivo*, dietary fish oil decreased the growth rate of MM by decreasing the cell proliferation rate and

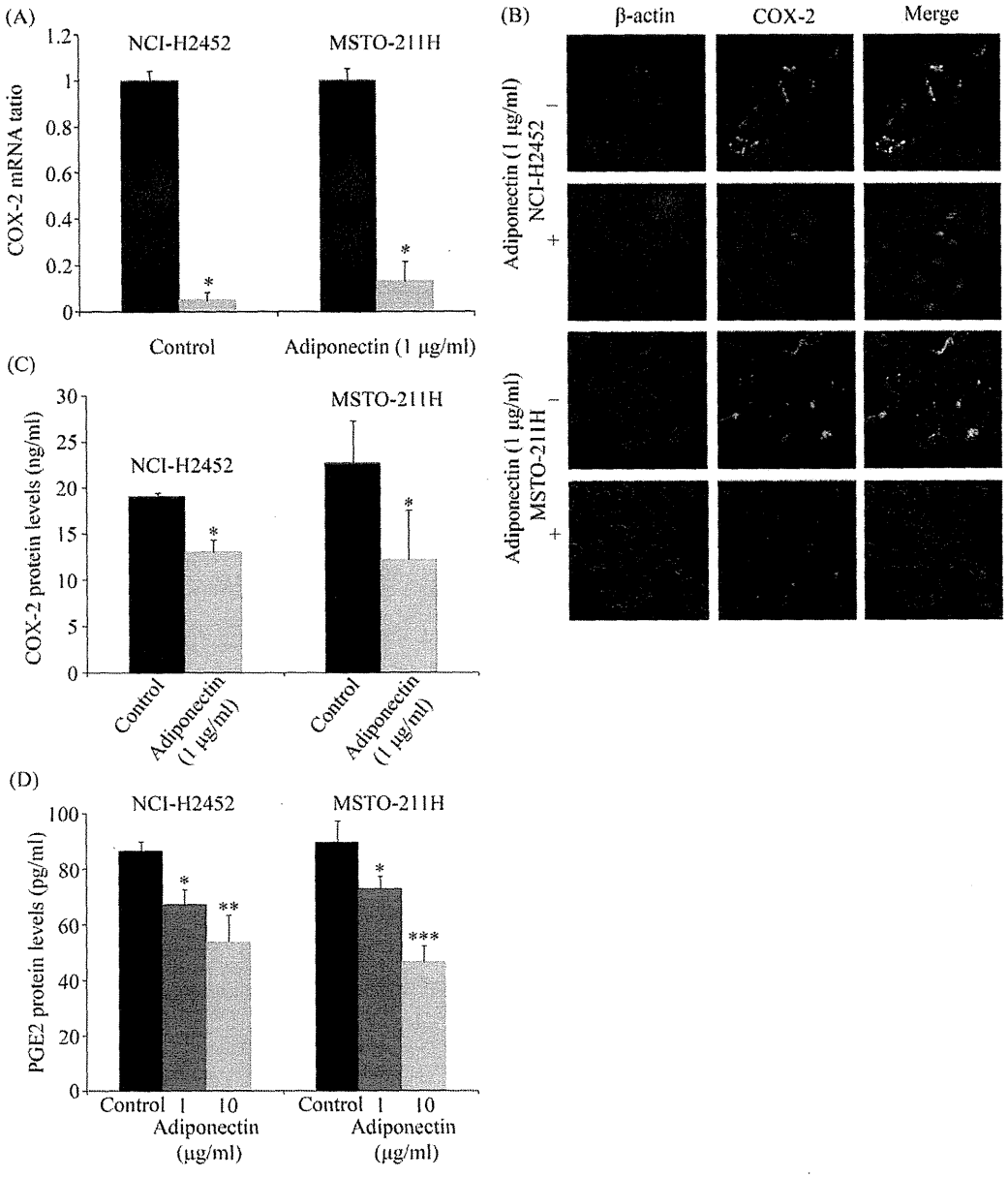

Figure 4. Effects of adiponectin on COX-2 or prostaglandin E2 (PGE_2) levels in MM cells. NCI-H2452 and MSTO-211H cells were treated with adiponectin (1 μg/ml) for 6 hours, and the mRNA (*A*), cell lysates (*C*), or culture supernatants (*D*) were isolated, or the cells were fixed (*B*). (*A*) The mRNA level of COX-2 was normalized by the 18 s rRNA level and analyzed by real-time RT-PCR. The expression levels of the genes in control are represented as 1. mRNA level of COX-2 was down-regulated by adiponectin treatment. (*B*) The immunocytochemistry was performed using anti–COX-2 antibody (*green*) and anti–β-actin antibody (*red*). Magnitude × 400. (C) COX-2 protein levels in cell lysates were determined by ELISA. (*D*) PGE_2 levels in the supernatant of the culture medium were determined by ELISA. *Columns* indicate the mean of three different experiments performed in triplicate. *Error bars*, SD. The significance of differences was calculated by *t* test.

increasing the number of apoptotic cells, which was accompanied by an increase in adiponectin and phospho-AMPK levels, and a decrease in a COX-2 level in the tumors. *In vitro*, adiponectin impaired the cell proliferation rate of MM cells. We showed that MM cells expressed both AdipoR1/R2, and these receptors were functional, as exposure of MM cells to adiponectin activated AMPK. We found that AMPK played an important role in COX-2/PGE_2 pathway regulation. Our results also suggest that adiponectin enhances AMPK activity and impairs the cell proliferation rate of MM cells, mainly via its receptor AdipoR1.

Compared with our results, previous studies have indicated that several molecular mechanisms, such as arachidonic acid–derived eicosanoid biosynthesis, transcriptional factor activation, increased or decreased production of free radicals and reactive oxygen species, and mechanisms involving insulin sensitivity and membrane fluidity, may mediate the anticancer actions of EPA and DHA (22). In addition to these mechanisms, our findings indicate a novel mechanism, adiponectin/AMPK/COX-2 pathway, to explain the association between fish oil and its anticancer actions.

Obesity has been shown to be associated with increased mortality for various cancers (23). Consistently, many studies have shown a positive association between adiposity and increased risk of cancers at multiple sites (24). Adiponectin, which is a peptide hormone secreted exclusively by the adipose tissue, may mediate the association between obesity and cancer. Several studies have shown that adiponectin inhibited the viability and increased apoptosis of acute myelomonocytic leukemia cell line M1 cells, acute monocytic leukemia cell line THP-1 cells, bovine capillary endothelial cells (9, 10), endometrial carcinoma cells (12), breast cancer cells (25), and prostate cancer cells (11). However, no previous study has shown the effect of adiponectin on the growth of MM or lung cancer cells. In the present study, MM cells were treated with adiponectin, and metabolically active cells were quantified. Adiponectin at concentrations of more than 5 μg/ml significantly impaired the cell proliferation rate of MM cells.

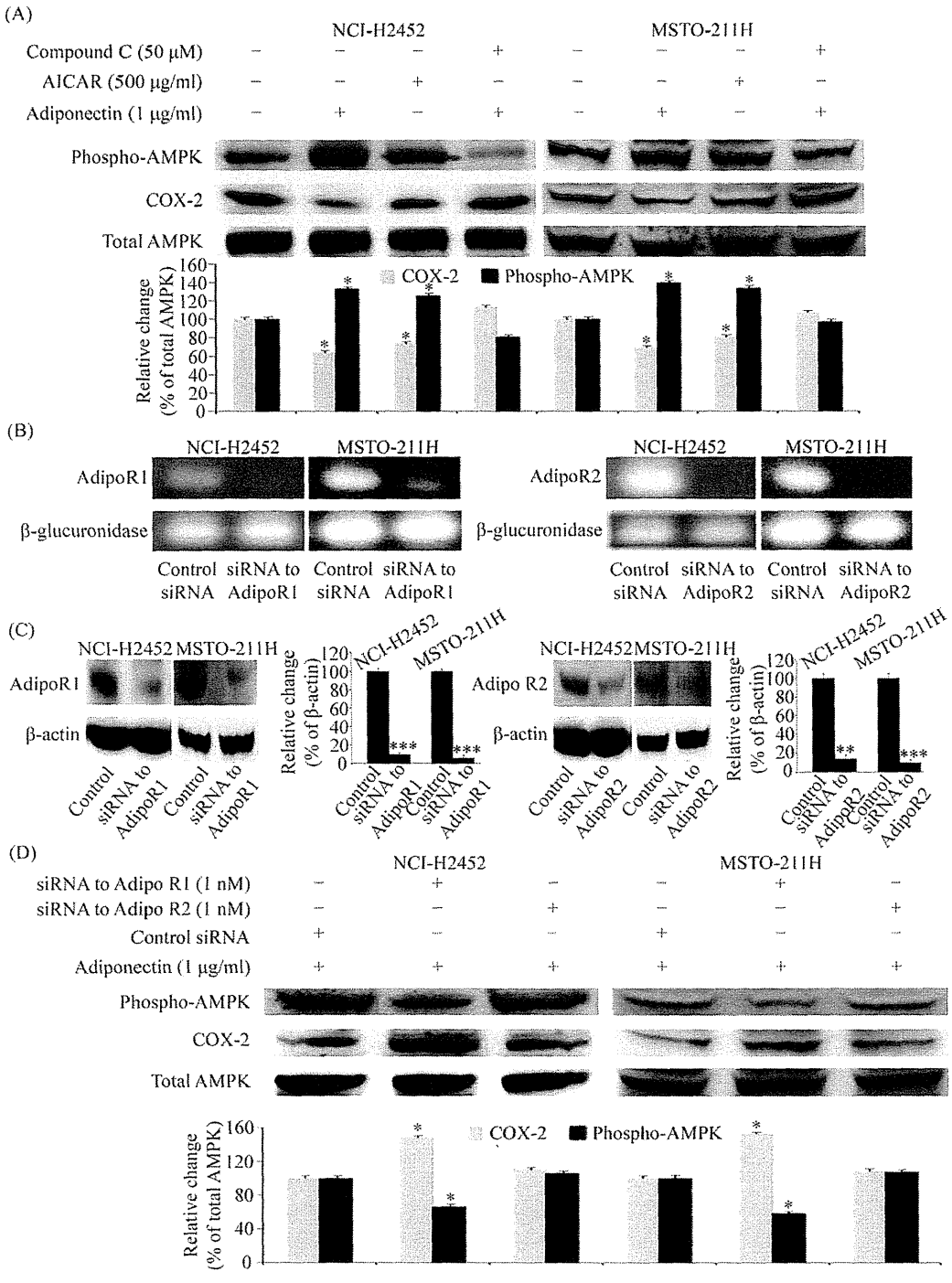

Figure 5. NCI-H2452 and MSTO-211H cells were treated with adiponectin (1 μg/ml) and 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR) (500 μg/ml) for the indicated concentrations for 6 hours. (*A*) NCI-H2452 and MSTO-211H cells were pretreated with compound C (50 μM) for 30 minutes, exposed to adiponectin (1 μg/ml) with or without AICAR for 6 hours, and then phospho-AMPK, COX-2, and total AMPK levels were detected by Western blot analysis. (*B–D*) The effects of adiponectin on phospho-AMPK or COX-2 levels in NCI-H2452 and MSTO-211H cells transfected with small interfering RNA (siRNA)–AdipoR1/R2. Total RNA was collected 24 hours after siRNA-AdipoR1/R2 or control siRNA transfection, and cell lysate was collected 48 hours after the transfection. (*B*) The relative levels of AdipoR1/R2 mRNA are shown by RT-PCR. β-glucuronidase is shown as a housekeeping gene. (C) The protein levels of AdipoR1/R2 were detected by Western blot analysis. The levels were quantified by a densitometry, normalized by β-actin, and shown graphically. (*D*) The cells transfected with siRNA were cultured with or without 1 μg/ml adiponectin for an additional 6 hours, and then the phospho-AMPK, COX-2, and AMPK proteins were detected by Western blot analysis. The optimized bands were quantified by densitometry, and are shown as the average of three independent experiments for phospho-AMPK, COX-2, and AdipoR1/R2 protein levels normalized to total AMPK bands (average ± SD; $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$).

The regulatory effect of adiponectin on COX-2 expression is controversial. On cardiac myocytes (26), bone marrow stromal cells (27), MS-5 stromal cells (28), and ovarian follicular cells (29), adiponectin elevated expression of COX-2. In contrast, several studies have suggested that, on some solid cancer cell lines, such as MCF-7 breast cancer cells (17) and colon cancer cells (15, 16, 18, 21), the AMPK activation decreased COX-2 expression level. Because adiponectin activated AMPK (13), it is hypothesized that adiponectin might suppress the expression of COX-2 via the AMPK pathway in MM cells. The current results suggest that adiponectin decreases COX-2 level via the AMPK pathway. These results, together with those of previous studies, suggest that the effect of adiponectin on COX-2 may be cell type specific. In this study, a possible mechanism by which AMPK might interact with COX-2 is unclear; further study is required to clarify the mechanism. Furthermore, the activation of the AMPK pathway has recently been implicated in the negative control of cell cycle progression (30, 31). Moreover, in various cell types, AMPK activation was reported to induce proapoptotic responses (32, 33). The COX-2 inhibitor, NS398, indicated dose- and time-dependent antiproliferative activity on MM cell lines (19). Taken together with our results, the anti–cell proliferation effect of adiponectin that we observed in MM cells might be mediated via the AMPK/COX-2 pathway.

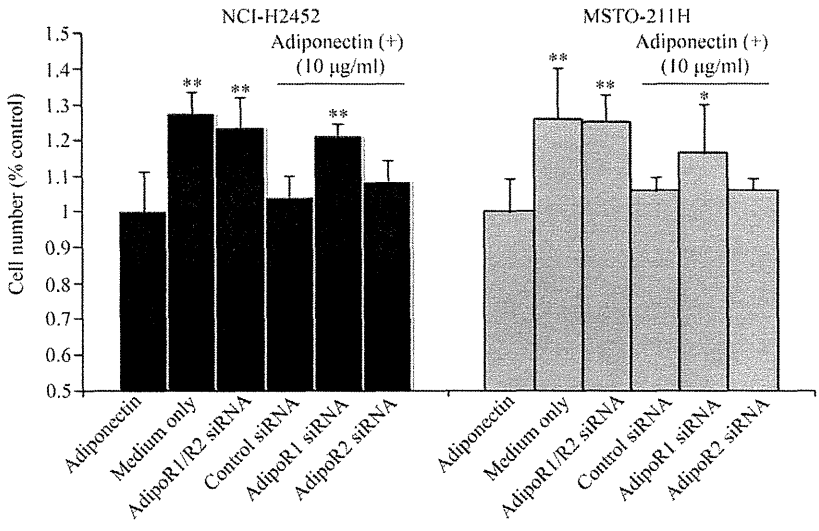

Figure 6. The effects of adiponectin on proliferation rate of siRNA-AdipoR1/R2–transfected cells. NCI-H2452 and MSTO-211H cells were cultured with 1 nM siRNA of AdipoR1, AdipoR2, or control for 48 hours. Then, NCI-H2452 and MSTO-211H cells were cultured with or without 10 μg/ml adiponectin for an additional 24 hours, and the cell proliferation rate was evaluated by WST assay. *Columns* indicate the mean of three studies performed in triplicate; *error bars*, SD. The significance of differences was calculated by ANOVA (*post hoc*, Tukey's method). $^{**}P < 0.01$ compared with the intact cells.

Two receptors for adiponectin, AdipoR1 and -R2, have been cloned in humans (34). AdipoR1 is known to be ubiquitously expressed at the highest levels in skeletal muscle, whereas AdipoR2 is predominantly expressed in skeletal muscle and the liver (34). A previous study reported functional differences between AdipoR1 and -R2 in the adiponectin-signaling pathway: AdipoR1 may be more tightly linked to the activation of AMPK pathways, whereas AdipoR2 seems to be associated with the activation of peroxisome proliferator–activated receptor-α (13). However, the tissue distribution and pathophysiological function of these two receptors are not fully understood. In this study, AdipoR1 and -R2 were expressed at considerable levels in MM cells. Adiponectin-induced AMPK activity was abolished by down-regulation of AdipoR1 by specific siRNA. In addition, the adiponectin-induced growth inhibition was significantly restored by AdipoR1 siRNA. Moreover, adiponectin-induced growth inhibition was similar to Meloxicam and NS398, which are inhibitors of COX-2. These data suggest that adiponectin regulates the AMPK/COX-2 pathway by AdipoR1. This pathway was associated with the adiponectin-induced growth inhibition in MM cells.

Adiponectin is an adipocytokine that is abundantly present in plasma at around 30 μg/ml in healthy humans, whereas levels below 4 μg/ml are associated with a coronary artery disease (35). Several studies have indicated that lifestyle modification increased serum adiponectin levels (36, 37). A case–control study showed that dietary habits are associated with the risk of MM (38). Our study suggests that the adiponectin-mediated AMPK activation and COX-2 down-regulation by the fish oil diet impair the growth rate of MM *in vivo* and *in vitro*. Thus, the current results may also have a positive impact on primary preventive medical strategies for people previously exposed to asbestos.

In conclusion, we found that a fish oil diet decreased the growth rate of MM, which was accompanied by an increase in adiponectin and phospho-AMPK activation levels, and a decrease in a COX-2 level, in xenograft MM mouse model. We demonstrate that MM cells express AdipoR1/R2 at the mRNA and protein levels. We also demonstrate that an adiponectin impaired growth rate of MM cells *in vitro* by activation of AMPK and down-regulation of downstream COX-2 expression. Adiponectin enhanced AMPK activity and impaired the proliferation rate of MM cells, mainly via its receptor, AdipoR1. These findings suggest that the induction or supplementation of adiponectin is an important tactic for therapeutic strategies for MM.

Author disclosures are available with the text of this article at www.atsjournals.org.

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こんなときどうする？
内科医のためのリハビリテーションセミナー

第9回 心臓①急性心筋梗塞後

森 信芳
東北大学病院内部障害リハビリテーション科
1997年弘前大学卒．同年，岩手県立胆沢病院に入職．心臓カテーテル治療を繰り返す患者の多さに，内科的・外科的治療だけでは対処しきれない患者の存在を意識し，2000年より東北大学大学院医学系研究科内部障害学分野に入室．2006年より現所属．

上月 正博
東北大学大学院医学系研究科障害科学専攻
1981年東北大学卒．初期研修で心臓リハに興味を抱く．内科医14年を経て，リハ科医に転向．2000年より同内部障害リハビリテーション科教授．内科とリハ科を融合した内部障害リハ医学・医療を確立し，普及に奔走中．総合内科専門医，リハ科専門医，腎臓専門医，高血圧専門医．日本リハ医学会理事，日本腎臓リハ学会理事長．

症例

(69歳，男性)

今回は心筋梗塞急性期加療後の退院困難症例を提示する．高血圧症，糖尿病，慢性腎不全(Cr 4.0 mg/dl)にて近医加療中．老人ホーム入所中であるが，日常生活動作(ADL)は自立していた．腹部大動脈瘤に対して8月30日に腹部大動脈ステントグラフト内挿術を施行された．

10月7日夜より嘔吐，下痢があり，8日早朝に本人より救急要請．当院来院時の所見などは以下のとおりである．

・胸部不快，呼吸困難あり．酸素10 l/分リザーバーマスクで投与し，SpO_2は100%であった．

・収縮期血圧は180 mmHg台であり，ペルジピン®2 mg静脈内投与するが血圧低下なく，持続投与を開始した．

・心エコー検査上，左室駆出率(LVEF)は約20%で，トロポニンT陽性，12誘導心電図上V_3～V_5でST上昇あり，急性心筋梗塞疑いにて緊急心臓カテーテル検査が実施された(図1)．左前下降枝#6～7に90%の狭窄を認めたため，薬剤溶出ステントを挿入したところ0%となった．右冠動脈#2 75%，左冠動脈主幹部#5 75%，左回旋枝#13 75%の残存狭窄あり．加療目的でCCU入院となる．

第8病日まで24時間持続透析を実施した．最高CPK 907 U/l，最高LDH 567 U/lと心筋梗塞による心筋の障害はそれほど大きくないことが示唆された．第9病日の心エコー検査ではLVEF 40%まで回復した．ベッド上安静の期間が長く，心筋梗塞急性期加療後の退院困難になる危険性のある症例として，第10病日にリハビリテーション(以下，リハ)科紹介，初診となった．

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【図 1】心臓カテーテル検査：左冠動脈治療前(左)・後(右)

(初診時機能評価)

リハ科初診時，血圧 122/54 mmHg，心拍数 77 bpm．左鼠径部に中心静脈栄養カテーテル留置，尿道カテーテル留置．ベッド上安静であった．意識は清明でコミュニケーションに問題なし．明らかな四肢麻痺なし．結膜貧血あり，黄染なし．左頸部血管雑音聴取，心雑音聴取せず，腹部血管雑音聴取．胸式呼吸．両足背動脈触知可能．

リハ専門医ならこうする

現在の安静度の確認，リスク因子の評価を行う．リハ科医師であれば，原因疾患，現在の状況にかかわらず発症前の生活状況をはじめに確認する．また，ライン類，特に座位，立位の妨げになる鼠径部のカテーテルは可能な範囲で早期に外す．

心筋梗塞急性期治療後の患者では，動脈硬化，低心拍出，ベッド上安静に伴うリスクとして起立性低血圧が考えられる．また，残存病変に起因する狭心症，虚血性心筋症による心不全のリスクをもつ．本症例では食事量が安定しており，中心静脈栄養カテーテルは抜去された．

●理学療法士への処方例

モニター下に理学療法を開始した．心筋梗塞急性期リハプロトコールは一般的には日本循環器学会のガイドライン[1]に準じて各施設で作成され，患者の安静度はすべての医療スタッフで共通の認識となっている(図2)．先に挙げたリスクの確認をしながら行う．初期評価としては，骨関節疾患などの除外のため，ベッド上で可動域制限の有無，徒手筋力テストによる筋力評価を行う．安静度の許す範囲の動作を，血圧，心拍数を確認しながら行っていく．本症例は心筋梗塞発症，経皮経管的冠動脈形成術から時間が経っており，さらに廃用症候群をきたしやすい状態であったが，徒手筋力テストの結果，ある程度下肢筋力も維持されていたため，体幹下肢筋力増強訓練，ベッドサイド座位訓練から開始した．腹部大動脈瘤治療からおよそ1カ月半の経過であり，急激な血圧変動を起こさないような動作の指導も必要であった．

●看護師への指示

心筋梗塞急性期リハプロトコールに基づき，病棟での自主トレーニングを促す．特に病初期には重要である．また，疾患の理解のための教育[2]を開始する．

●本人・家族への生活指導

一般的な心臓リハの教育プログラムに則り，