Journal of Cardiology Cases 7 (2013) e24–e26

Contents lists available at www.sciencedirect.com

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

Estrogen is involved in improvement of impaired cardiac glucose uptake in cancer patients

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ARTICLE INFO

Article history:
Received 15 June 2012
Received in revised form
18 September 2012
Accepted 27 September 2012

Keywords:
Cancer
Glucose uptake
Estrogen
Fluorodeoxyglucose positron emission tomography/computed tomography

ABSTRACT

We previously demonstrated that inflammatory stress impaired cardiac glucose uptake, using fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) by showing that a proportion of patients with subtle FDG signals was remarkably increased compared with that of normal subjects. The current study assessed the inhibitory effects of cancer-associated stress on cardiac glucose uptake in female cancer patients, and compared the results with those obtained for healthy female subjects. Cardiac glucose uptake was decreased in female cancer, as indicated by the significantly higher number of patients with poor FDG uptake and the lower number of patients with high FDG uptake, compared with the number of healthy subjects with poor and high FDG uptake, respectively. These results suggest that cancer-associated stress inhibited cardiac glucose utilization. From the 78 female cancer patients, 13 oophorectomized patients, who underwent repeated postoperative follow-up examinations by FDG-PET/CT before and after receiving hormone replacement therapy (HRT) with estrogen derivatives, were analyzed to determine the effects of estrogen on cardiac glucose uptake. HRT increased a proportion of patients with high FDG signals to comparable in healthy subjects with high FDG uptake, whereas that of patients with poor FDG uptake decreased. These results suggest that estrogen can improve cardiac glucose uptake in cancer-resected and oophorectomized patients.

<**Learning objective:** This study presents us a new point of view, which should be taken into account on the pathophysiology in some cardiovascular diseases, the sex-differences of energy substrates for the heart, i.e., estrogen or its derivatives accelerates the preference of glucose by the heart. Unfortunately, a very few studies have studied on this issue, e.g., effects of sex-steroid on cardiac uptake of energy substrate, and therefore, this suggests that cardiologists do not focus on this issue.>

Introduction

In the previous study, we reported that systemic inflammation impairs cardiac glucose uptake, suggesting that in addition to psychological stress, inflammatory stress itself remarkably affects glucose utilization in cardiomyocytes. In that study, the number of patients with inflammation, who exhibited poor cardiac fluorodeoxyglucose (FDG) uptake, was significantly higher than that of healthy controls with poor FDG uptake [1]. These results supported the concept raised by Ansari [2] that the pathophysiology of Takotsubo cardiomyopathy may be more complicated than expected and that in addition to the speculated pathophysiological factors including coronary microvascular dysfunction and reduced coronary flow, another key factor may also be involved, namely the poor utilization of energy substrates (glucose) necessary for optimal cardiac performance [1,2]. Inflammation and carcinogenesis are well-known major stressors in the human body and many substances including cytokines, which have been implicated in the development of cachexia, are found in the blood of cancer patients independent of cancer stage. However, few studies have investigated the effects of cancer-associated stress on cardiac glucose uptake and glucose metabolism. To investigate stressful conditions other than inflammatory stress, the present retrospective study focused on the effect of cancer-associated conditions on cardiac glucose utilization.

One of the characteristic features of Takotsubo cardiomyopathy is female predominance. Therefore, many animal and human studies have been conducted to determine the protective

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http://dx.doi.org/10.1016/j.jccase.2012.09.009

effects of estrogen and its derivatives against stress-induced cardiomyopathy [3–7]. These studies have mainly focused on the inhibitory effects of estrogen on cell death caused by reactive oxygen species and on hypothalamo-sympatho-adrenal outflow. The effects of estrogen on enhanced gene expression of cardioprotective molecules have also been covered. However, the effects of estrogen on the regulation of cardiac energy metabolism, especially on cardiac glucose uptake, remain to be elucidated. In this study, the extent of cardiac glucose uptake was determined in female cancer patients and compared with that in apparently healthy female subjects. Then, the effects of estrogen supplementation on cardiac glucose uptake were evaluated using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging.

Methods

The data obtained by FDG-PET/CT imaging, a specific method of evaluating cardiac glucose utilization, are known to be profoundly affected by variation in glucose levels. To overcome data variability as much as possible, examinations at our university hospital are routinely performed after patients have fasted for more than 12 h. To investigate the effects of cancer-related stress on cardiac glucose uptake, we examined PET scores of 78 female cancer patients ($n = 78$; age, 47 ± 12 years) with no past history of diabetes mellitus (DM). The PET score, developed for semi-quantitative assessment of cardiac glucose uptake in our previous study [1], was also used in the present study. These scores were assigned according to the level of FDG uptake, as follows: score 0, a faint FDG signal in the entire transverse section of the mid-portion of the left ventricle, which demonstrates a ring form; score 1, a signal with characteristics intermediate to those representing scores 0 and 2; and score 2, a homogeneous, intense signal throughout the ring. Our previous study clearly demonstrated that despite adjustment for the variability in FDG signals, PET scores of 0 were always observed in a proportion of normal controls (10–15%). The locations of cancer in the study patients were as follows: ovary ($n = 14$), uterine cervix ($n = 15$), uterus ($n = 4$), breast ($n = 2$), colon ($n = 5$), stomach ($n = 7$), esophagus ($n = 2$), thyroid ($n = 2$), blood ($n = 3$), and miscellaneous sites ($n = 24$). Patients with end-stage cancer were not included. For comparison, PET/CT examinations were also performed in a control group including 121 age-matched (51 ± 10 years) apparently healthy subjects, who reported no history of inflammatory diseases, heart diseases, or DM in a medical questionnaire and underwent PET/CT to exclude malignancy as part of personally requested health check-ups during the same period. Before PET/CT examination, written informed consent, which was approved by the ethics committee of Kochi Medical School Hospital, was obtained from all the patients and healthy subjects.

In another retrospective study, we also focused on the effects of hormone replacement therapy (HRT) with estrogen derivatives, which was postoperatively started in 13 oophorectomized patients, who had been treated for ovarian or uterine cervical cancer. These patients were among those included in the first part of the study evaluating the effects of stress on cardiac glucose uptake. These patients had no history of coronary, infectious, metabolic diseases, or chronic renal failure. No patients were identified to show cardiac dysfunction. The chemotherapy regimens applied to these 13 patients included carboplatin, cisplatin, paclitaxel, vincristine, and mitomycin C. No anthracyclines, which are well-known to be cardiotoxic, were included. HRT for these oophorectomized patients was usually started during chemotherapy. Therefore, PET/CT was performed to evaluate cardiac glucose uptake rather during ongoing or following chemotherapy.

Statistical analysis was performed as follows. Differences in the proportional trend in PET scores between the controls and cancer patients were evaluated by using the chi-square test, and changes in PET scores in the cancer patients before and after HRT were assessed by the Wilcoxon t-test. In both tests, differences were considered to be significant at $p < 0.05$.

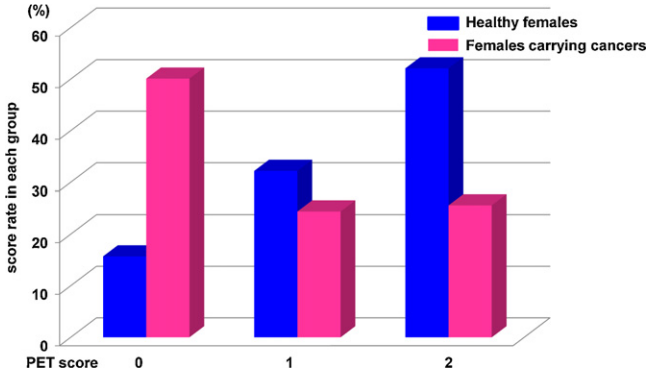

Fig. 1. Cardiac glucose uptake is decreased in cancer patients compared with that in healthy, age-matched female controls. The prevalence of a PET score 0 is higher while that of score 2 is reciprocally lower in cancer patients than in healthy controls. PET, positron emission tomography. (For interpretation of the references to color in the text, the reader is referred to the web version of the article.)

Results

Fig. 1 shows that in the female cancer patients (pink column), the prevalence of PET scores 0, 1, and 2 were 50.0%, 24.4%, and 25.6%, respectively. In contrast, in the age-matched, apparently healthy females ($n = 121$) (blue column), PET scores of score 0, 1, and 2 were 15.7%, 32.2%, and 52.1%, respectively. These results indicated that the number of cancer patients with a PET score of 0 was significantly higher than the number of controls with the same score (15.7% vs. 50.0%; $p < 0.01$; Chi-square test). On the other hand, score of 2 was more frequent in the controls than in the cancer patients (52.1% vs. 25.6%; $p < 0.01$; Chi-square test).

As previously mentioned, 13 female patients (age, 49 ± 10 years; red column) suffering from ovarian or uterine cervical cancer, who underwent bilateral oophorectomies, were retrospectively selected from those evaluated in the first part of the study. Postoperatively PET/CT examinations were repeatedly performed both before and after HRT with estrogen derivatives. The effects of HRT in these 13 patients were evaluated using PET/CT. As shown in

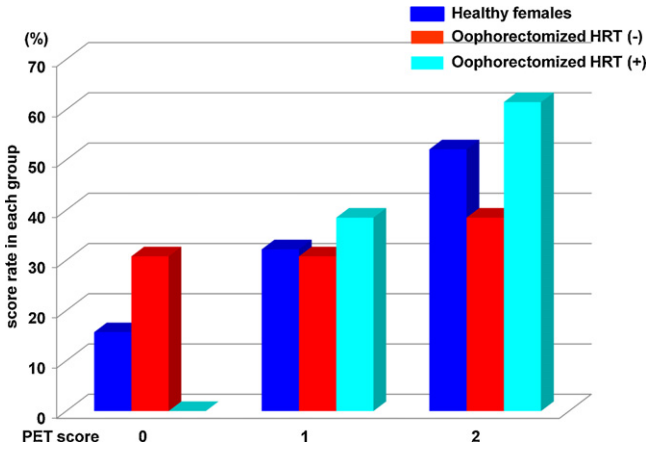

Fig. 2. In 13 female patients who underwent cancer resection followed by oophorectomy, restoration of glucose uptake levels following hormone replacement therapy (HRT) with estrogen derivatives was exhibited. After HRT the prevalence of a PET score 0 is lower while that of score 2 is higher. PET, positron emission tomography. (For interpretation of the references to color in the text, the reader is referred to the web version of the article.)

Fig. 2, the prevalence of patients with scores 0, 1, and 2 were 30.8% ($n = 4$), 30.8% ($n = 4$), and 38.5% ($n = 5$), respectively (red column). Before HRT, these 13 patients showed an increased prevalence of the score 0 and a reciprocally decreased prevalence of the score 2 compared with that in the controls (blue column). After HRT, however, the prevalence of score 0 decreased from 30.8% to 0%, while that of score 2 increased from 38.5% to 61.5% in the cancer patients (Fig. 2, light blue column; $p < 0.05$; Wilcoxon t-test), thus becoming comparable between the cancer patients and controls.

Discussion

The present study suggests that female cancer patients have impaired cardiac glucose uptake, suggesting that cancer-associated stress suppresses efficient cardiac glucose utilization. This was indicated by differences in the prevalence of PET scores between 78 female cancer patients and 121 age-matched, healthy female controls (Fig. 1). This study also suggests that estrogen is involved in the restoration of cardiac glucose uptake (Fig. 2). Studies investigating the risk factors of cardiovascular diseases have revealed that women in the reproductive phase of their life are at a low risk of cardiovascular diseases. However, onset of menopause and loss of ovarian function are associated with a significant increase in the prevalence of diseases such as coronary heart disease. Many studies have asserted the beneficial and cardioprotective effects of estrogen, including anti-apoptosis, anti-cardiac remodeling, and modulation of calcium signaling. However, studies have not yet confirmed the efficacy of HRT in preventing cardiovascular events. Some controversy exists over the modulating effects of estrogen on cardiac glucose metabolism in human hearts. FDG-PET/CT may be useful in fully investigating these effects. One study found that glucose utilization was not affected by estrogen, but fatty acid utilization was affected by estrogen [8]. The present retrospective study despite its small patient population and endogenous nature suggested a novel pathophysiological mechanism of Takotsubo cardiomyopathy other than conventional stress, which includes psychological stress that directly activates catecholamine release.

Takotsubo cardiomyopathy was initially observed in typical circumstances of psychological stress and was represented by a catecholamine surge. However, cases of Takotsubo cardiomyopathy in the absence of psychosocial stress have also been reported. In those cases despite difference in underlying diseases, the common feature of impaired cardiac glucose uptake was identified by FDG/PET analysis [9,10]. Cancer-associated cachexia induces a cytokine storm; but in contrast, elevated catecholamine levels cause insulin resistance. On a superficial level, the pathophysiological features of these conditions seem to be distinct. However, based on the results of the present FDG study, impaired cardiac glucose utilization may be a common downstream phenomenon shared by conditions of different etiology.

Cancer may be a specific stressor that impairs cardiac glucose uptake in a manner similar to inflammation, that is, through the activity of proinflammatory cytokines, including tumor necrosis factor, as previously reported in our study [1]. Impaired glucose utilization may cause inadequacies in cardiac glucose metabolism when the demand for glucose is abrupt, as in the case of pathological insults. HRT may therefore be beneficial for the restoration of impaired cardiac glucose metabolism. Considering the present results and the fact that Takotsubo cardiomyopathy predominantly occurs in females, we suggest that estrogen enhances glucose utilization and provides adequate energy substrates to cardiomyocytes. These mechanisms may cause resistance of cardiomyocytes to apoptosis. Therefore, estrogen may play a pivotal role in arresting the development of Takotsubo cardiomyopathy in female cancer patients.

According to the results of the current study, HRT contributes to enhanced glucose uptake. This result in patients with tumor resection followed by oophorectomies suggests that estrogen plays a positive role in cardiac glucose uptake. This suggestion is also supported by the fact that Takotsubo cardiomyopathy is more often seen in middle-aged, especially menopausal females. In addition, cardiomyopathy observed in oophorectomized rats with restraint stress was partially reversed by estrogen therapy [3,5]. A cascade connecting estrogen with enhanced glucose uptake may occur during the process of glucose utilization in the heart.

The small population in this study is a limitation that must be overcome in a future study by enrolling more patients to confirm the hypothesis suggested here. Future *in vitro* studies will investigate the direct effects of estrogen on glucose utilization of cardiomyocytes.

Acknowledgments

This work was partially supported by Grants-in-Aid for Scientific Research from the Japan Science and Technology Agency and the Japanese Ministry of Education, Culture, Sports, Science and Technology (No. 23590678).

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