Reply to “Letter to the Editor: ‘Low-dose whole body irradiation: a potential therapeutic modality’”

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In their letter (17), Chander M. Pathak and Krishan K. Khanuja commended the findings of our paper (27). We are grateful to them for highlighting the clinical relevance and important implications of our research. However, two issues require clarification.

First, we did not simultaneously investigate the temporal long-term impact of whole body low-dose radiation (WB-LDR) on both pancreatic and renal tissue in diabetic animals (27). One reason is that we focused on the preventive effect of WB-LDR on diabetic kidney. With this goal in mind, all animals in the study were treated with multiple low doses of streptozotocin (STZ), which destroyed pancreatic β-cells before WB-LDR was given. However, studies by others suggest that WB-LDR at 0.5 Gy gamma rays, administered either before alloxan-induced diabetes or in NOD mice with spontaneously developed diabetes, leads to upregulation of pancreatic antioxidants (22, 23). There was also a study indicating that chronic exposure of type 2 diabetic db/db mice to LDR significantly upregulated pancreatic antioxidants along with reduction of glucose levels (24). These findings suggest that WB-LDR can induce pancreatic antioxidant upregulation, resulting in certain preventive effects on diabetic complications, but this hypothesis has yet to be specifically tested. We recently demonstrated that STZ-induced diabetes significantly reduces systemic (plasma) and testicular antioxidants (catalase and superoxide dismutase) and then showed that repeated WB-LDR (25 or 50 mGy X-rays) in posthyperglycemic diabetic rats significantly prevented reduction of diabetes-induced systemic and testicular antioxidants and also prevented diabetes-induced testicular cell death and oxidative damage (28).

The second issue is that we did not explore the optimal conditions for WB-LDR to effectively protect the kidney from diabetes. The authors pointed out that the application of moderate doses (between 3 and 6 Gy) for therapeutic purposes to diabetic patients appear to be unacceptable to the scientific community, since with application of higher radiation doses acute toxic effects and potentially late long-term effects are expected. Unlike high and middle doses of ionizing radiation, LDR induces few detrimental effects and significantly stimulates cellular metabolism and enhances cell defense function, which is known as hormesis and adaptive response (2, 3, 12, 25). The hormetic and adaptive response includes the stimulation of DNA, RNA, and protein synthesis as well as DNA repair activity, the increase in cellular antioxidant capacity, the prolongation of life span, and the activation of immune functions. Whether LDR can be considered as an alternative approach to preventing diabetes and diabetic complications has been questioned (25). In the study under discussion here, however, we demonstrated that accumulated dose 0.175 Gy at week 2 and 0.35 Gy at week 4 can significantly protect the kidney from diabetes-induced inflammation, dysfunction, and oxidative damage. At higher radiation doses (0.70 Gy at week 8 and 1.4 Gy at week 16), there was no further protective effect (27). Therefore, we need to further explore the minimal accumulated dose range that can effectively protect the kidney from diabetes.

We are grateful to these authors for providing an important reference that Yamaoka and Komoto (26) reported that the Misasa Hot Spring treatment with radon significantly improved vasodilatation and alleviated diabetic symptoms, which is the first evidence in humans of LDR efficacy. In animal studies, the WB-LDR has been found not only to decrease the incidence and percentage of developing diabetic mice, but also to enhance the survival rate of type 1 and type 2 diabetic animals (9, 11), which might be related to the prevention of diabetic complications. Recent studies have demonstrated that single (9) or repetitive exposures (27, 28) of diabetic animals to WB-LDR can significantly reduce diabetes-induced pathological damage in the brain, kidney, and testis as well as the heart (C. Zhang, X. Li, and L. Cai, unpublished data). More interestingly, repetitive exposure of diabetic rats can significantly accelerate diabetic wound healing process as a therapeutic approach (W. Guo et al. unpublished data). All of these animal studies and human data strongly suggest that LDR may be useful in either the prevention or treatment of diabetes in the clinic.

To date, a few groups have performed clinical phases I and II trials with WB-LDR for cancer patients and shown the effective enhancement of the therapeutic efficacy for non-Hodgkin’s lymphoma without increase in toxic effects (5, 13, 18–20), and even clinical phase III trail has been proposed (20). These studies suggest that appropriate use of LDR can offer beneficial effects to cancer patients under certain conditions.

There is another important question: Does LDR contribute cancer risk? A report (4) summarized 15 country studies with a total of 407,000 radiation workers followed for over 20 years, providing 5.2 million person-years of follow-up, shows that 90% of those workers received a dose less than 50 mGy, which contributed an excess relative risk for all-cause mortality that was 0.42/Gy (0.042/100 mGy) in 20 years. Two other recent cohorts of medical workers in Canada (67,562 and 337,397, respectively) showed that mortality from cancers and non-cancer diseases for those exposed to less than 100 mGy was generally below that expected from the general Canadian population (29, 30). It is known that radiation doses contributed by various computed tomography (CT) scans vary in a wide range from 10s to 100s mSv (here we consider mSv equal...
there is a need to evaluate the application of LDR as either by whole body or specifically targeted organ region; noninvasive, cheaper, easily delivered, and able to be given within CT dose range) for diabetic patients; “then we should significant beneficial effect of LDR (25 or 50 mGy, likely the US (6). Current annual usage is estimated to be more than century has risen about 12-fold in the UK and about 20-fold in information (1, 11). In fact, CT usage over the past quarter of a scans were canceled after the parents received the risk infor-
mentation in terms of lifetime risk that is dependent on age at the
time of exposure and the type of CT scan administered.
However, generally speaking, the risk appears to be very small.

Do these low potential risks scare the parents? A study showed that when parents were informed about CT risks, their willingness to have their child undergo CT did not significantly change, although they became more willing to consider other imaging options if they were equally effective (11). No CT scans were canceled after the parents received the risk information (1, 11). In fact, CT usage over the past quarter of a century has risen about 12-fold in the UK and about 20-fold in the US (6). Current annual usage is estimated to be more than three million scans per year in the UK and more than 60 million per year in the US (6). Therefore, as pointed out by Pathak and Khanduja, “It is clear that none of the medications used in clinical practice is absolutely nontoxic,” if there is a significant beneficial effect of LDR (25 or 50 mGy, likely within CT dose range) for diabetic patients; “then we should accept the same without any radiation phobia in the mind.” In addition, given that there are several advantages of LDR compared to other antiabetic or cardiovascular medications: noninvasive, cheaper, easily delivered, and able to be given either by whole body or specifically targeted organ region; therefore, there is a need to evaluate the application of LDR as realistic and parallel, as is done for other therapeutic modalities.

DISCLOSURES
No conflicts of interest are reported by the authors.

REFERENCES
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