Abstract
The purpose of this study is to evaluate the effects of ultraviolet blood irradiation on the blood when a low dose of ultraviolet C (UV-C) is directly irradiated to the blood in a diabetic rabbit model and to evaluate the effects on treatment for diabetes. Type 1 diabetics were induced by intravenous (IV) injection of alloxan monohydrate 110 mg/kg into New Zealand white rabbits weighing 2 - 2.5 Kg. A UV-C lamp with light intensity of 4 W and wavelength of 260 nm was used to irradiate UV to the blood. After 10 ml blood was collected from diabetic rabbits and UV was irradiated to the blood, UV irradiated blood was transfused back to the original rabbits. The ultraviolet blood irradiation (UBI) treatment was performed a total of 8 times. We evaluated the effects of the UBI treatment on diabetes through hematological analysis before and after UBI treatment were performed. Our results indicate that the reduced body weight is increased and blood glucose levels are significantly reduced after the UBI treatment is performed when compared to those prior to the UBI treatment. In addition, HCO₃⁻ levels and blood pH were elevated and lowered, respectively. Increased ALT and AST levels are reduced by 25.8 % and 17.8 %, respectively, when compared to those prior to the UBI treatment. In addition, CRE, BUN and UA levels indicating renal functions are significantly reduced when compared to those prior to the UBI treatment. In addition, serum Mg²⁺ and Ca²⁺ concentrations are significantly increased when compared to those prior to the UBI treatment. Serum K⁺ concentration is significantly reduced when compared to that prior to the UBI treatment. As the results of calculating AG and osm, they are significantly reduced when compare to those prior to the UBI treatment. When the UBI treatment is performed in a diabetic rabbit model, our results indicate that blood glucose levels are reduced. Hematological analysis demonstrates that the UBI treatment is effective to alleviate the diabetes.

**Keywords:** Ultraviolet blood irradiation; Type 1 diabetes rabbit model; blood glucose level; Alanine amino transferase (ALT); Aspartate aminotransferase (AST); Creatinine (CRE); Blood urea nitrogen (BUN); Uric acid (UA)
Introduction

Once it enters the 20th century, the most innovative invention in medical history is various antibiotics such as penicillin, steroids and vaccines. The invention of antibiotics and steroids is very effective in treatments for acute inflammatory diseases, but there are some side effects such as occurrence of resistant bacteria against antibiotics and adverse effects of steroid hormones. With regard to current medicine of the 21st century, advanced professional therapeutic methods are being developed to treat incurable diseases and rare diseases using genetic analysis and stem cells. However, there are still many diseases which cannot be treated by above professional therapies. In addition, there are new diseases, expression of antibiotic resistant bacteria and various syndromes which cannot be identified nor treated by the modern medicine[1-5].

As a new therapeutic method, the therapy using UV light was studied and applied in the clinical trials in the US and Western countries until the 1950’s. The therapeutic methods using UV light were not studied any longer in the US and Western countries. However, it has taken the place as a field of medical technology through active research and clinical trials in Germany and Russia[6-12]. Researchers are actively conducting the research on the new therapeutic method in the US, Russia and China and are trying to develop it as a new clinical therapeutic method[9,13-18]. Research on this therapy is actively being conducted in the world but the fundamental mechanism for the therapy has not been understood. Many clinical studies on the therapy have been conducted and thousands of research papers have been published[19-26].

Diabetes emerges as the disease causing social problems, because it has a very high[27] prevalence as a typical chronic metabolic disease. Diabetes goes beyond endemic limits and is approaching epidemic proportions globally[28,29]. Diabetes is a metabolic disease with high blood glucose levels caused by the metabolic disorder resulting from defects of hormones such as insulin, glucagon or glucocorticoids involved in the metabolism of glucose or by abnormal reactions in the pathway[29]. Because the diabetes is characterized by high blood glucose levels, which leads to a wide range of malfunctions in the metabolic control over carbohydrates, proteins, fats and electrolytes, it is closely associated with increases in various chronic degenerative diseases[30]. It has been known that secondary complications such as diabetic retinopathy, neuropathy and nephrosis are caused when high blood glucose levels are sustained in diabetic patients. Thus, it is important to control blood glucose levels when diabetic patients are treated[31,32]. Despite development of modern medicine, the diabetes is not fully cured. Diet, exercise therapy, drug therapy, and insulin injection are being used as the treatments for diabetes. Many studies on the development of new diabetic therapeutic agents are being conducted[33-35]. Oral hypoglycemic agents and insulin formulation for the treatment for the diabetes are continuously developed. However, because it is the chronic disease which is not fully cured once patients develop diabetes, it causes a serious problem[36].

Thus, in this study, we would like to evaluate the effects of ultraviolet blood irradiation on the diabetes by using physical methods with UV light rather than drug therapy such as insulin injection in order to get over diabetes causing serious problems.

Materials and Methods

Design of ultraviolet blood irradiation device

In this study, we have produced the ultraviolet blood irradiation (UBI) device to identify effects of ultraviolet blood irradiation on the blood in a diabetic animal model. Figure 1 shows a simple drawing and photo of the UBI device. In brief, a fixing holder for quartz crystal cuvette is installed in the center and ultraviolet (UV) lamps are installed on both sides of the holder. The UV lamps are designed to adjust the distance (5 mm ~ 120 mm) from the holder in the center. The UV lamps on both sides of the holder are installed in parallel to form an angle of 180° with the holder. The reason is that the intensity of light source from a lamp is the highest when it forms an angle of 180° with the lamp. A timer is installed to control the UV irradiation time. When it reaches a setup time, it is turned off automatically. G4T5 TUV 4W Germicidal Fluorescent Light Bulb (Philips, USA) with the wavelength of 260 nm is used as the UV lamp. A circular quartz crystal cuvette is produced in length of 150 nm, thickness of 1 mm, and inner diameter of 4 mm. Both ends of the cuvette can be connected to syringes. One end of the quartz crystal cuvette is connected to the input syringe in order to irradiate UV to the collected blood. The blood passes through the cuvette at a constant flow rate by using the syringe pump (Model: LSP01-1A, Longer Pump® China). Ultraviolet blood irradiation is performed in the cuvette. Once UV is irradiated to the blood, the blood is collected in the syringe in other side of the cuvette. The quartz crystal cuvettes with thickness of 1, 2, 3 and 4 mm are used to measure the intensity of light source irradiated from the UV lamp based on the distance and to measure UV transmission intensity based on the thickness of the quartz crystal cuvettes. The UV transmission intensity is measured at each spot with various distances from 5 mm to 100 mm between the lamp and quartz crystal cuvette. To measure UV transmission intensity, a ST-512 UV Light meter (Sentry Optronics Corp. Taiwan) is attached on the surface of quartz crystal.

Figure 1: Schematic illustration and photographic of the ultraviolet blood irradiation device.
Experimental animals

Adult male twelve New Zealand white rabbits of body weighing 2 - 2.5 kg were used in the study. All the rabbits were kept in cages with wide square mesh at the bottom to avoid coprophagy and maintained under controlled conditions of humidity, temperature (22 ± 2°C) and 12 hours light and dark cycle. Food and water were provided ad libitum. They were fasted for 18 hours prior to the experiment, allowing free access to water only. The experimental protocols were approved by the Institutional Animal Ethics Committee. All experimental protocols (CBU2013-0010) were approved by the Committee on the Care of Laboratory Animal Resources, Chonbuk National University and were conducted in accordance with the Guide for the Care and Use of Laboratory[37].

Induction of experimental diabetes - Procedure for injecting alloxan monohydrate

The 12 rabbits weighing between 2 to 2.5 kg were made diabetic by injecting intravenously 110 mg/kg body weight of alloxan monohydrate (A7413, Aldrich)[38-40]. Before giving alloxan, the normal blood glucose levels of all rabbits were estimated. After 2 hours of alloxan injection the 5% Dextrose injected to the all-diabetic rabbits intraperitoneally to prevent a hypoglycemic condition of rabbits with alloxan. After 72 hours of alloxan injection, the blood glucose levels of all surviving rabbits were determined by the glucose oxidase method.

Ultraviolet blood irradiation treatments

It is confirmed that the diabetes is induced by measuring blood glucose levels in rabbits at 72 hours after alloxan is injected. The blood is collected from diabetic rabbits after 1 week. The UBI treatment is performed to the blood. For the UBI treatment, UV is irradiated to the blood collected through auto transfusion and the blood is transfused back to the original rabbit. Anticoagulation Sodium Citrate Solution (BOIN ACDA SOLN, SBD Co., Ltd.) is used to prevent coagulation of the blood when it is collected. 10 ml blood is collected from the vein by using 20 ml syringe. UV light with the intensity of 10.290 J/cm² is irradiated to the blood which passes at a constant flow rate using the syringe pump in the UBI device. After the UBI treatment is performed, the blood is transfused back to the original rabbit. The UBI treatment is performed a total of 8 times. Rabbits are stably raised in a laboratory animal breeding facility. Food and water are sufficiently supplied.

Blood sampling

Blood samples were collected from the ear marginal veins of the all animals at 24 hr intervals for up to three days, and then every week up to 18 weeks. Sera were isolated from blood samples in tubes with no anticoagulant, after being clotted for 30 min, and centrifuged at 2000 G for 5 min.

Biochemical analysis

Blood was collected from the ear marginal vein. Blood collection, storage, and measurement were performed as previously described. A Nova Stat Profile® pH Ox® Ultra analyzer (NOVA Biomedical Corp., Waltham, MA, USA) was used to measure the levels of lactate, pH, HCO₃⁻, hemoglobin, hematocrit, ionized magnesium (Mg²⁺), calcium (Ca²⁺), potassium (K⁺), and chloride (Cl⁻) in freshly collected whole blood. As previously described(Kwon et al. 2010), the anion gap values were calculated by the formula, (Na⁺ - (Cl⁻ + HCO₃⁻)).

After clotting, blood serum was separated by centrifugation at 3000 rpm for 20 min. The levels of glucose (Glu), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphates (ALP), lactate dehydrogenase (LDH), creatinine kinase (CK), albumin, total cholesterol (TC), total protein (TP), triglyceride (TG), high-density lipoprotein (HDL), low density lipoprotein (LDL), creatinine (CRE), blood urea nitrogen (BUN), and uric acid (UA) were analyzed using a Model 020 auto analyzer (Hitachi, Tokyo, Japan). Osmolality (Osm) values were calculated by the formula, (1.86 × Na⁺ + (Gluose/18) + (BUN/2.8) + 9) as previously described[41].

Histological Analysis

For histological analysis, the pancreases were dissected from all of the study groups at the end of experiment period. The tissues were washed in normal saline, cut into pieces of the desired size, and fixed in 10% neutral buffered formalin solution. After fixation, the samples were cleaned and embedded in paraffin. Tissue sections of 5 μm thickness were mounted on slides, stained with hematoxylineosin, and examined on a light microscope.

Statistical analysis

Data are expressed as means ± standard errors of the mean (SEMs). Differences between groups were evaluated by analysis of variance (ANOVA) with the bonferroni post hoc test or by calculation of Spearman’s rank correlation coefficient, as appropriate, using Prism 5.03 (Graph Pad Software Inc., San Diego, CA, USA). Statistical significance was set at p < 0.05.

Results

UV penetration intensity

Figure 2 shows the results of measuring the UV penetration intensity based on the distance between the UV lamp and quartz crystal cuvette with various thicknesses. As shown in the figure, the intensity of UV light irradiated from the UV lamp tends to decrease with increasing distance from light source as a function (Intensity of illumination = 14.476 × exp (-x/19.6) + 0.98 (R²: 0.997)) on without the quartz crystal. As the result of measuring transmission intensity at the spot with a distance of 10 mm from the UV lamp, the UV intensity without the quartz crystal is 9.531±0.2759 mW/cm². The intensity of UV light penetration through the quartz crystal with thickness of 1 mm is 8.575 ± 0.3563 mW/cm², which is reduced by 10 %. The intensity of UV light penetration through the quartz crystal with thickness of 2, 3, and 4 mm is 8.358 ± 0.3132, 7.959 ± 0.3137 and 7.853 ± 0.3209 mW/cm², respectively. It is significantly reduced.

According to the study of Wiesner and Bernstein[42], it was effective to use the quartz crystal cuvette with the thickness of 1 mm used in the UBI treatment since the quartz crystal cuvette with the thickness of about 1 mm was developed[43,44]. In this study, we select the distance between the quartz crystal cuvette and light source in 10 mm and the thickness of the quartz crystal cuvette in 1 mm on the basis of results of previous studies.
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Figure 2: The results of measuring the UV transmission intensity based on the distance between the UV lamp and quartz crystal cuvette with various thicknesses. No: no quartz crystal, Q1: 1 mm thickness quartz crystal, Q2: 2 mm thickness quartz crystal, Q3: 3 mm thickness quartz crystal, Q4: 4 mm thickness quartz crystal.

Effects of the UBI treatment on body weight and glucose levels

Figure 3 shows changes in body weight and blood glucose levels of diabetic rabbits before and after the ultraviolet blood irradiation (UBI) treatment is performed. As the results, body weight does not decrease on day 3 after alloxan injection. The Glu level significantly decreases after the UBI treatment is performed. Glu level is 433.3 ± 118.3 mg/dL over 8 weeks after the UBI treatment is discontinued. It significantly decreases when compared to that prior to the UBI treatment.

Figure 3: Effects of ultraviolet blood irradiation treatments on the body weight (a), whole blood concentration and serum levels of glucose (Glu) (b) in alloxan-induced diabetic rabbits. Data are reported as means ± SEMs (n = 12). *: p < 0.05; **: p < 0.01; and ***: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus the BD (Before alloxan-induced diabetic); #: p < 0.05; ##: p < 0.01; and ###: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus the NUBI (Before ultraviolet blood irradiation treatments procedure).

Organ harvest

Figure 4 shows the conditions of organs in diabetes rabbits that do not undergo the UBI treatment and undergo the UBI treatment after diabetes is induced. The stomach and bladder become abnormally small in the diabetic rabbit that do not undergo the UBI treatment. The pancreas is substantially damaged. In addition, left renal becomes abnormally swollen. While it is taken out, a large amount of urine is leaked. After swollen left renal is excised, it is reduced as small as right renal. When the inside of the left renal is observed by naked eyes, many tissues are damaged when compared to those in the right renal. Thus, it seems to be unable to play its roles. However, when organs of rabbits undergoing the UBI treatment are observed by naked eyes, their conditions are much better than those in rabbits that do not undergo the UBI treatment.

Figure 4: Photos of the organ without UBI treatments procedure rabbit (a) and with 8th times UBI treatments procedure rabbit (b).

Effect of the UBI treatment on the liver function by serum metabolic enzymes analysis

Figure 5 shows results of liver function tests such as serum alanineaminotransaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and alkaline phospha-
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tase (ALP) to examine the efficacy of the UBI treatment on the diabetes in a diabetic rabbit model. However, increased ALT and AST levels caused by alloxan injection were reduced by 21.6% and 14.6%, respectively, while the rabbits undergo the UBI 8 times treatments. ALT and AST levels were reduced by 25.8% and 17.8%, respectively, over 8 weeks after the UBI treatment is discontinued. LDH levels were decreased by 26% while the rabbits undergo the UBI 8 times treatments. Over 8 weeks after the UBI treatment is discontinued, LDL levels were as low as other levels prior to alloxan injection. In addition, ALP levels were decreased by 45.2% while the rabbits undergo the UBI 8 times treatments. Over 8 weeks after the UBI treatment is discontinued, the levels were significantly decreased when compared to those before the UBI treatment is performed.

Effect of the UBI treatment on the renal function by serum metabolic enzymes analysis

Figure 6 shows results of renal function tests such as serum creatinine (CRE), blood urea nitrogen (BUN) and uric acid (UA) to examine the efficacy of UBI treatment on the diabetes in a diabetic rabbit model. The levels were significantly decreased when compared to those before the UBI treatment is performed. CRE, BUN and UA levels were 0.958 ± 0.173, 33.31 ± 4.11 and 3.075 ± 0.245 mg/dL, respectively, over 8 weeks after the UBI treatment is discontinued. The levels were significantly decreased when compared to those before the UBI treatment is performed.

Figure 7 shows total cholesterol (T-CHO), high density lipoprotein (HDL); low density lipoprotein (LDL), low density lipoprotein (c); TG, triglyceride (d); T-PRO, total protein (e); Alb, Albumin (f). Data are reported as means ± SEMs (n = 12). *: p < 0.05; **: p < 0.01; and ***: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus the BD (Before alloxan-induced diabetic); #: p < 0.05; ###: p < 0.01; and ####: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus NUBI (Before ultraviolet blood irradiation treatments procedure). BD: Before alloxan-induced diabetes, UBI: Before ultraviolet blood irradiation treatments procedure, 8th; After 8th times treatments procedure of ultraviolet blood irradiation, A8; After 8th times treatments procedure 8 weeks later.

Effects of the UBI treatment on serum lipid and protein levels

Figure 7 shows total cholesterol (T-CHO), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG), total protein (PRO-T) and Albumin (Alb) levels in the blood to examine the efficacy of UBI treatment on the diabetes in a diabetic rabbit model. However, increased T-CHO, LDL and TG levels by alloxan injection were reduced by about 37%, 24%, and 25%, respectively, while the rabbits undergo the UBI 8 times treatments. T-CHO, LDL and TG levels were reduced by about 52%, 20% and 31%, respectively, over 8 weeks after the UBI treatment is discontinued. On the other hand, prior to alloxan injection, HDL, T-PRO and Alb levels were 34.0 ± 4.49, 6.825 ± 0.77 and 4.633 ± 0.5 mg/dL, respectively. HDL, T-PRO and Alb levels in the diabetic rabbit model induced by alloxan injection were 26.08 ± 3.26, 5.025 ± 0.694 and 3.85 ± 0.408 g/dL, respectively. The levels were significantly decreased when compared to those prior to alloxan injection. However, HDL, T-PRO and Alb levels in the diabetic rabbit model undergoing the UBI 8 time treatments were 30.33 ± 3.47, 6.517 ± 0.694 and 4.438 ± 0.368 g/dL, respectively. The levels were significant-
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Data are reported as means ± SEMs (n = 12). *: p < 0.05; **: p < 0.01; and ***: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus the BD (Before alloxan-induced diabetic); #: p < 0.05; ##: p < 0.01; and ###: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus NUBI (Before ultraviolet blood irradiation treatments procedure). BD: Before alloxan-induced diabetes, NUBI: Before ultraviolet blood irradiation treatments procedure, 8th; 8th times treatments procedure of ultraviolet blood irradiation, A8; After 8th times treatments procedure 8 weeks later.

Table 1: Effects of ultraviolet blood irradiation treatments on the blood ionized hydrogen concentration (pH), bicarbonate anion (HCO₃⁻), dioxide partial pressure (pCO₂), oxygen partial pressure (PO₂), oxygen saturation (SO₂), hemoglobin concentration (Hb), and hematocrit value (Hct) in alloxan-induced diabetic rabbits.

|               | BD            | NUBI                        | 8th            | A8            |
|---------------|---------------|-----------------------------|----------------|---------------|
| pH (-)        | 7.369 ± 0.045 | 7.262 ± 0.07***             | 7.388 ± 0.045### | 7.421 ± 0.035### |
| HCO₃⁻ (mmol/dL) | 23.5 ± 3.565 | 17.25 ± 1.766***            | 22.77 ± 2.564## | 23.12 ± 1.879### |
| pCO₂ (mmHg)   | 28.94 ± 0.857 | 38.44 ± 2.891***            | 33.8 ± 3.777### | 34.6 ± 3.227### |
| pO₂ (mmHg)    | 79.56 ± 4.443 | 63.88 ± 8.894##             | 71.33 ± 4.524## | 71.92 ± 3.711### |
| SO₂ (%)       | 95.33 ± 3.842 | 91.76 ± 2.305###            | 94.02 ± 1.187## | 94.31 ± 0.0808### |
| Hb (g/dL)     | 12.35 ± 0.4858| 10.99 ± 0.6396***           | 11.51 ± 0.193### | 11.25 ± 0.206### |
| Hct (g/dL)    | 37.00 ± 1.633 | 31.69 ± 1.251***            | 33.23 ± 1.301### |

Data are reported as means ± SEMs (n = 12). *: p < 0.05; **: p < 0.01; and ***: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus the BD (Before alloxan-induced diabetic); #: p < 0.05; ##: p < 0.01; and ###: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus NUBI (Before ultraviolet blood irradiation treatments procedure). BD: Before alloxan-induced diabetes, NUBI: Before ultraviolet blood irradiation treatments procedure, 8th; 8th times treatments procedure of ultraviolet blood irradiation, A8; After 8th times treatments procedure 8 weeks later.

Table 2: Effects of ultraviolet blood irradiation treatments on the blood electrolyte balance in alloxan-induced diabetic rabbits.

|               | BD            | NUBI                        | 8th            | A8            |
|---------------|---------------|-----------------------------|----------------|---------------|
| Na⁺ (mmol/dL) | 135.7 ± 3.575 | 141.3 ± 3.125###            | 132.4 ± 3.515### | 133.7 ± 3.52### |
| Cl⁻ (mmol/dL) | 97.90 ± 6.712 | 104.3 ± 2.293##             | 97.6 ± 12.684### | 97.3 ± 23.212### |
| Mg²⁺ (mmol/dL) | 0.609 ± 0.0626| 0.505 ± 0.0340###           | 0.557 ± 0.032## | 0.569 ± 0.0692### |
| Ca²⁺ (mmol/dL) | 1.418 ± 0.0587| 1.294 ± 0.0576###           | 1.515 ± 0.1627### | 1.578 ± 0.1597### |
| K⁺ (mmol/dL)  | 4.459 ± 0.4036| 5.616 ± 0.496               | 4.702 ± 0.3991### | 4.593 ± 0.3103### |
| AG (mmol/dL)  | 14.25 ± 10.98 | 19.71 ± 3.423               | 11.99 ± 3.951# | 13.21 ± 3.207 |
| Osm (mMg)     | 277.8 ± 6.557 | 321.0 ± 8.793###            | 294.0 ± 4.908### | 294.1 ± 9.978### |

Data are reported as means ± SEMs (n = 12). *: p < 0.05; **: p < 0.01; and ***: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus the BD (Before alloxan-induced diabetic); #: p < 0.05; ##: p < 0.01; and ###: p < 0.001, Bonferroni post hoc test following one-way ANOVA versus NUBI (Before ultraviolet blood irradiation treatments procedure). BD: Before alloxan-induced diabetes, NUBI: Before ultraviolet blood irradiation treatments procedure, 8th; 8th times treatments procedure of ultraviolet blood irradiation, A8; After 8th times treatments procedure 8 weeks later.

Effects of the UBI treatment on blood gas

Table 1 represents the results of measuring ionized hydrogen concentration (pH), bicarbonate anion (HCO₃⁻), dioxide partial pressure (pCO₂), oxygen partial pressure (pO₂), oxygen saturation (SO₂), hemoglobin concentration (Hb), and hematocrit value (Hct) in whole blood to examine the efficacy of UBI treatment on the diabetes in a diabetic rabbit model. When pH is measured in the blood, the pH is significantly lowered in the diabetic rabbit model induced by alloxan injection when compared to that prior to alloxan injection. However, the pH is significantly elevated in the diabetic rabbit model undergoing the UBI 8 times treatments when compared to that prior to alloxan injection. The pH is significantly elevated over 8 weeks after the UBI treatment is discontinued when compared to that prior to alloxan injection. Serum HCO₃⁻ levels which were closely associated with changes in pH in the blood were significantly decreased in the diabetic rabbit model induced by alloxan injection when compared to that prior to alloxan injection. However, the HCO₃⁻ levels were significantly increased in the diabetic rabbit model undergoing the UBI 8 times treatments when compared to that prior to alloxan injection. The HCO₃⁻ levels were significantly increased over 8 weeks after the UBI treatment is discontinued when compared to that prior to alloxan injection. The pH is significantly decreased over 8 weeks after the UBI treatment is discontinued when compared to that prior to alloxan injection. In addition, as the results of measuring oxygen partial pressure (pO₂), oxygen saturation (SO₂), Hb and Hct, levels were significantly decreased in the diabetic rabbit model induced by alloxan injection when compared to those prior to alloxan injection. However, the levels were significantly increased in the diabetic rabbit model undergoing the UBI 8 times treatments when compared to that prior to alloxan injection. The levels were significantly increased over 8 weeks after the UBI treatment is discontinued when compared to that prior to alloxan injection.
Effects of the UBI treatment on the blood electrolytic balance

Table 2 represents the results of measuring ions in whole blood to examine the efficacy of UBI treatment on the diabetes in a diabetic rabbit model. Na\(^+\) and Cl\(^-\) concentrations in the diabetic rabbit model induced by alloxan injection were significantly increased when compared to those prior to alloxan injection. However, the Na\(^+\) and Cl\(^-\) concentrations were significantly decreased in the diabetic rabbit model undergoing the UBI 8 times treatments when compared to that prior to alloxan injection. The Na\(^+\) and Cl\(^-\) concentrations were significantly decreased over 8 weeks after the UBI treatment is discontinued when compared to those prior to alloxan injection. Mg\(^{2+}\) and Ca\(^{2+}\) concentrations were significantly increased when compared to those prior to alloxan injection. However, the Mg\(^{2+}\) and Ca\(^{2+}\) concentrations were significantly increased in the diabetic rabbit model undergoing the UBI 8 times treatments when compared to those prior to alloxan injection. Mg\(^{2+}\) and Ca\(^{2+}\) concentrations were significantly increased over 8 weeks after the UBI treatment is discontinued when compared to those prior to alloxan injection. K\(^+\) concentration in the diabetic rabbit model induced by alloxan injection is significantly increased when compared to those prior to alloxan injection. However, the K\(^+\) concentration is significantly decreased in the diabetic rabbit model undergoing the UBI 8 times treatments when compared to that prior to alloxan injection. The K\(^+\) concentration is significantly decreased over 8 weeks after the UBI treatment is discontinued when compared to that prior to alloxan injection. Results of calculating the AG and Osm in the diabetic rabbit model induced by alloxan injection indicate that AG and Osm levels were increased when compared to those prior to alloxan injection. However, the AG and Osm levels were significantly decreased in the diabetic rabbit model undergoing the UBI 8 times treatments when compared to that prior to alloxan injection. The AG and Osm levels were significantly decreased over 8 weeks after the UBI treatment is discontinued when compared to those prior to alloxan injection.

DISCUSSION

Previous studies have reported that blood Glu levels are reduced by rapid oxidization of Glu caused by the elevation of ATP (increase in glycolysis) in red blood cells when the UBI treatment is performed. Body temperature rise and energy elevation are accompanied[10,45,46]. In this study, we do not find the elevation of ATP caused by the UBI treatment but we found reductions in blood Glu levels. Thus, we conclude that the UBI treatment is effective for diabetes. As the UBI treatment is characterized by promoting the metabolism of glucose based on energy, it is expected to affect the diabetes in some way. Early American doctors performed the UBI treatment to treat patients with diabetes. According to the clinical study of Miley[16], blood glucose levels of a patient with diabetes drop from 350 – 400 to 140 – 150 after the UBI treatment is performed twice. 3 – 4 weeks later after the UBI treatment is discontinued, the blood glucose levels are elevated back to the previous levels. However, in a patient with insulin dependent diabetes, the blood glucose levels are controlled for 18 months only by performing the UBI treatment without insulin. He has also advised that hypoglycemic shock should be prevented by decreasing dose of insulin when the UBI treatment is performed[47]. Frick et al. report that blood glucose levels are lowered and the efficiency of insulin is improved when the UBI treatment is performed. In addition, 58 patients with diabetic retinitis undergo the UBI treatment and then achieve good outcomes, because the aggregation of red blood cells is inhibited. 70 % of patients in the stage 2 and 20 % of patients in the stage 3 improve vision[49].

As an indicator of damage of the liver functions, ALT and AST are usually present in the liver but they are introduced into the blood when the liver is damaged[10,45,46]. It is reported that levels are increased when the diabetes is induced[50]. In this study, it is found that ALT and AST levels are increased in a diabetic rabbit model induced by alloxan injection. However, it is found that ALT and AST levels are reduced in a diabetic rabbit model undergoing the UBI treatment.

Lactate dehydrogenase (LDH). It plays a role as a factor to predict the interference of normal actions of the cells induced by pathological inflammation. In particular, LDH promotes the conversion of glucose into energy in the cells and is found in almost all body organs including pancreas[51,52,53]. In addition, the increase in levels of LDH isoenzymes is a symptom of various diseases. In particular, it is a symptom of pancreatitis[54]. In damaged cells, the membrane is broken and thus release of LDH is increased[55]. Results of this experiment demonstrate that the LDH levels are increased in a diabetic rabbit model. It is thought that the elevation of LDH is caused by the increases in cell death with increasing cell necrosis. However, it is found that the LDH levels are reduced in a diabetic rabbit model undergoing the UBI treatment[56].

Alkaline phosphatase (ALP) is a hydrolase enzyme responsible for removing phosphate groups in an alkaline environment. It is determined whether the bile duct which runs from the liver to the duodenum is defect by measuring ALP levels. In addition, it is determined that the bone is properly formed or

Histological analysis

Histological analysis of diabetic rabbits treated with UBI revealed comparatively less beta-cell granulation and reduced pancreatic islet vacuolation compared with diabetic control rabbits (Figure 8A). Without UBI treatments procedure alloxan-induced diabetic rabbits exhibited extensive degranulation of beta-cells and severe vacuolation of the pancreatic islets (Figure 8B).

Figure 8: Histological findings in the pancreas (H-E staining, ×200). A; with 8th times UBI treatments procedure alloxan-induced rabbit, B; without UBI treatments procedure alloxan-induced rabbit, Red circle; pancreatic islets, Black scale bar =100 µm.
the liver or placenta normally functions by measuring the ALP levels. ALP activity can be elevated by closure of the liver or bile duct caused by diabetes and its complications[67]. As shown in the results of experiment, blood pH is lowered in a diabetic rabbit model induced by alloxan injection. Therefore, since the ALP which is an enzyme hydrolyzing phosphate groups does not play its role in an alkaline pH, its level is high. However, the ALP level is not reduced in a diabetic rabbit model undergoing the UBI treatment. The reason is that ALP levels are reduced because cause blood pH is elevated by the UBI treatment and thus hydrolysis of phosphoric compounds is promoted by increasing ALP activity. In addition, ALT, AST and LDH levels which are indicators of liver functions are increased in a diabetic rabbit model, but increased levels tend to decrease by the UBI treatment. Our results showed enhancement of liver function in diabetic rabbits undergone UBI treatment, which agreed with[58] Who found that Phototherapy causes little improvement in intrinsic liver function, Robert et al[59]. Found that no significant changes in serum alkaline phosphatase, SGOT, albumin, or total protein occurred from the control period to the end of the study in human patients subjected to phototherapy. Olney reported that 31 out of 43 patients with acute hepatitis, patients received only the kon technique of blood irradiation. 22 patients were followed up to four years, 60% of patients were clinically recovered[60].

In normal people, proteins are metabolized and most of them are finally excreted as urea in the renal. Urea is excreted through the renal as the final product of protein and amino acid metabolism. BUN is blood urea nitrogen and it is mostly filtered and excreted in glomerulus of the renal. However, some of BUN is re-absorbed depending on the water contents in the body, which is affected by amounts of protein intake, amounts of urine and gastrointestinal bleeding. Because blood urea level is high when the renal function is poor, blood BUN level is one of indicators evaluating renal function[60]. The results of experiments indicate that blood BUN level is high in a diabetic rabbit model but BUN level tends to decrease in the diabetic rabbit model undergoing the UBI treatment.

The results of this experiment indicate that CRE, BUN and UA levels which are indicators of renal functions are high in a diabetic rabbit model induced by alloxan injection but these levels are reduced in a diabetic rabbit model undergoing the UBI treatment. The reason could be that some parts of renal tissues are lost in the initial stage of diabetes but loss of the tissue is prevented by performing the UBI treatment. In addition, when the kidney of laboratory animals is taken out and observed by naked eyes, many areas of the renal are damaged in rabbits that do not undergo the UBI treatment. The kidney is not damaged in rabbits that undergo the UBI treatment. Through such results, we expect that loss of the renal caused by diabetes is prevented by performing the UBI treatment.

There are three kinds of cholesterols in the blood such as HDL-cholesterol (high-density lipoprotein cholesterol) which prevents arteriosclerosis by removing cholesterol in the blood and tissues, LDL-cholesterol (low-density lipoprotein cholesterol) which causes heart diseases and stroke by promoting arteriosclerosis, and triglyceride (TG)[61]. TG levels are increased when large amounts of carbohydrates are ingested. High TG levels cause heart diseases, stroke and diabetes[62,63]. In diabetes, insulin in adipose tissues interferes with TG metabolism by inhibiting hormone sensitive lipase. Thus, degradation of fats is increased, which elevates levels of fatty acids and glycerol. In the nutritional conditions of healthy people, glycerol 3-phosphate is re-esterified back to TG after the fats are degraded. In the diabetes, the cycle is blocked, because glycerol 3-phosphate is not sufficiently produced from glucose and thus it cannot be used. The glucose is introduced into adipose cells and then is released into the blood due to decreases in re-esterification of fatty acids. In addition, while the glucose is accumulated in the extracellular liquid, which induces high blood glucose levels in the diabetes, glucose levels are low in muscles and adipose cells. Insulin stimulates synthesis of glycogen and increases synthesis of glucokinase. Without insulin, the synthesis of glycogen is inhibited and degradation of glycogen is promoted in which glucose is transported into the blood from the liver, which causes high blood glucose level[64]. In the diabetes, like metabolic syndrome, hyperlipidemia causes the increases in LDL cholesterol, decreases in HDL cholesterol, hypertriglyceridemia and increases in small dense LDL cholesterol. It worth mentioning that, there are few researches pertaining effect of UBI on hyperlipidemia. However, defects in lipid metabolism can be relieved when blood glucose levels are properly controlled. It has been reported that T-CHO levels are increased together with decreases in HDL-cholesterol ratio and increases in lipids in the blood due to defects in lipid metabolism caused by defects in carbohydrate metabolism in diabetes[65,66]. As shown in the results of experiments, TG levels are elevated in a diabetic rabbit model induced by alloxan injection. However, the blood TG levels were not lowered in a diabetic rabbit model undergoing the UBI treatment. The reason is that the UBI treatment promotes the circuit of re-forming TG by increasing and re-esterifying glycerol 3-phosphate produced from glucose. In addition, increased T-CHO and LDL levels in a diabetic rabbit model induced by alloxan injection are reduced by performing the UBI treatment. Decreased HDL, T-PRO and Alb levels in a diabetic rabbit model tend to increase in the diabetic rabbit model undergoing the UBI treatment. In recent years, Zaleskay et al. have performed the study on patients with heart disease. According to the results of their study, elevated cholesterol levels and LDL levels are lowered through the UBI treatment. According to the results of the study on patients with chronic diseases, pO2 can be increased and pCO2 can be decreased by performing the UBI treatment. In addition, LDL levels can be lowered[67,68]. The UBI treatment was very effective in, many diseases including diabetes and hypertension[69].

The human body keeps a neutral condition at about pH 7.4. As a number of acids are produced in the body by various activities such as respiration and metabolism, the pH may be lowered. However, variations in the pH are minimized by many buffering systems[70-72]. As the pH is lowered by 0.1, H+ is usually reduced by 80 %. Three mechanisms control H+ ion. First one is a chemical buffer present in ECF and ICF. Second one is removal of H+ through the renal. Among them, removal of H+ by ECF buffer occurs the most rapidly. Removal renal is followed. Representative substance of ECF buffer is bicarbonate ion (HCO3-)[73]. Most (60 %) of carbon dioxide is transported in the blood as the form of bicarbonate ion (HCO3-). The rest of carbon dioxide is transported to the lung in the form bound to proteins or hemoglobin present in the blood as a physically dissociated state. The body maintains a neutral pH by appropriately controlling the buffering process. If the re-absorption
capacity declines due to the defects in the renal, blood HCO₃⁻levels are lowered and the body produces excessive amounts of acids, which lowers the pH. Results of experiments indicate that blood pH and HCO₃⁻levels are lowered and pCO₂ is increased in a diabetic rabbit model induced by alloxan injection. However, decreased pH and HCO₃⁻levels are increased and blood pCO₂ is reduced by performing the UBI treatment.

Our result agreed with Matt man and Lida[74] who found that UB blood irradiation improved oxygen delivery, blood elements, stimulation of mitochondrial oxidation may help quick recovery of many aliments.

The insulin secretion is directly associated with calcium. Concentration of calcium is normally ten thousand times higher outside of β-cells than inside[16,75-81]. Upon stimulation, calcium enters the β-cells and thus promotes the insulin secretion. German cell physiologists Erwin Neher and Bert Sakmann[82-85] found that the reason why the insulin is not released from the pancreas when blood glucose level is elevated is that calcium ions cannot enter the β-cells due to defects in the path.

Potassium (K) is an essential cation to help nerve cells act properly and muscles contract smoothly. Moreover, it is involved in enzymatic reactions as a component of cell membrane and it is involved in the metabolism of glucose or protein. If potassium concentration is elevated, insulin deficiency or diabetic keto-acidosis may appear.

Magnesium (Mg) is the fourth most abundant cation in the body and the second most abundant cation in the cell[86]. Because it is the cation mainly in the cells, measurement of magnesium in serum or plasma does not represent the whole amounts in the body. Even if measured magnesium concentration is normal in the plasma, the deficiency of magnesium cannot be ruled out[87]. It has been widely known that hypokalemia and hypocalcaemia may be caused by hypomagnesaemia[88,89]. The hypomagnesaemia is common in patients with the diabetes. In particular, it occurs more often in patients who have a history of chronic alcohol consumption[47].

As shown in the results of experiments, concentrations of Na⁺, Cl⁻ and K⁺ are increased in the blood of the diabetic rabbit model. Our result is differ from these results could be attributed to that, they directly correlate between hypokalemia and hypocalcaemia as a sequel of low magnesium level induced by chronic alcohol consumption. Liver may heavily affected by alcohol consumption as well. The concentrations tend to decrease in the diabetic rabbits undergoing the UBI treatment. In addition, concentrations of Mg²⁺ and Ca²⁺ are decreased in the blood of the diabetic rabbit model. The concentrations tend to increase in the diabetic rabbits undergoing the UBI treatment.

Also, our results agreed with Petrosyan et al.[90], who found that dogs with high blood pressure developed hypopon- tremia and hypochromia, increase in activities of ALT, AST, creatine phosphokinase, and alkaline phosphates. They concluded that osmolality was significantly decreased. Parameters of electrolyte and osmotic homeostasis most rapidly returned to normal as well in animals subjected to UBI. Significantly increased urea, creatine, ALP, cholesterol and lipoproteins were reduced and returned to normal by up 10-30 days in dogs treated with UBI indexes of water and electrolyte balance and urea concentration most rapidly return to normal in animals exposed to UV irradiation of the blood.

Conclusions

This study is the preliminary study to evaluate the effects of ultraviolet blood irradiation on diabetes in a type 1 diabetic rabbit model by using the auto transfusion. We evaluated the effects of the UBI treatment on diabetes through hematological and biochemical analysis of diabetic rabbits by performing the UBI treatment. We found that UBI Improved glucose level, body weight, liver and kidney functions. In addition to osmolarity and electrolytes homeostasis were enhanced.

Therefore, as the UBI treatment can lower the blood Glu levels and prevent the damage of the renal, liver and pancreas, UBI could be very effective in the diabetes. However, further studies are needed in which molecular mechanisms including cell signaling and ion channels of UBI-treated animals are monitored.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2015R1D1A3A01019245).

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