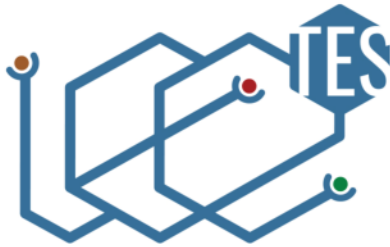




UNIVERSITAS
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1ST INTERNATIONAL CONFERENCE
ON EMERGING ISSUES IN TECHNOLOGY,
ENGINEERING AND SCIENCE

PROCEEDINGS

1-2 JULY 2021

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Jong Seong Kang

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Ratnadewi

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BRIEF CONTENTS

INVITED SPEAKERS	IV
ORGANIZING COMMITTEES	V
PROGRAM COMMITTEE	VII
FOREWORD	IX
CONTENTS	XI

INVITED SPEAKERS

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FOREWORD

Message from the Rector



Honorable Keynote Speaker, Mr. Ignasius Jonan, former Minister of the Energy and Mineral Resources, and previously Minister of the Transportation Ministry of the Republic of Indonesia, we are greatly honored to have you with us this morning.

Distinguished keynote speakers, Prof. Ahmad M. Ramli (represented by Ikhsan Baidirus, S.H., LL.M., Director of Post, General Directorate of Post and Information Technology, Ministry of Communication and Information Technology), Prof. John Silke, Dr. Ferry Sandra, Prof. Takayuki Arai, Prof. Young Ho Kim, Prof. Susy Tjahjani, Prof. Pim Martens, Dr. Dwinita Larasati, Prof. Chien-Hsu Chen, Prof. Wilson Bangun and Prof. Marcellia Susan, as well as all participants in the international conferences at Maranatha University.

A very good morning and best wishes to you all, and good evening to our colleagues in the US. Greetings and a warm welcome to Maranatha Christian University (MCU), Bandung, Indonesia.

I am delighted to be here with you today for the opening of the first MCU international conferences. These are: (i) The International Conference on Emerging Issues in Technology, Engineering, and Science, and (ii) The International Conference on Emerging Issues in Humanity Studies and Social Sciences, with the themes of: Digital Ecosystems for Sustainable Health and Community Development towards an Intelligent Society, and Innovations for Sustainable Community Development - Research and Practices, respectively.

We thank the many participants from countries across the different continents: the USA, the UK, the Netherlands, Norway, Taiwan, Japan, Korea, Thailand, Singapore, Malaysia, India, Australia, and New Zealand.

These first international conferences will serve as a platform to enable speakers and participants to share their research results, drawn from up-to-date research work, to initiate and strengthen further collaboration.

Without further ado, I would like to thank all the participants who have joined us for these international conferences. Again, my sincere hope is that what we accomplish today will be beneficial towards establishing collaboration among all the participants of these conferences.

I hereby declare the first international conferences at MCU in 2021 officially open.

May God bless you all. Thank you.

Prof. Ir. Sri Widiyantoro, MSc., PhD., IPU.
Rector of Maranatha Christian University

Foreword



On behalf of the committee members, it is a great pleasure to welcome you all to our first two international conferences: Emerging Issues in Technology, Engineering, and Science (ICE-TES) and, Emerging Issues in Humanity Studies and Social Sciences (ICE-HUMS).

ICE-TES and ICE-HUMS are twin events which serve our passion in balancing technology and humanity issues in the world of science and share the core values of our university: Integrity, Care & Excellence (ICE).

This year's theme for both conferences focus on the United Nations' Sustainable Development Goals (SGD), which emphasize the following aspects: ICE-TES (Digital Ecosystem for Sustainable Health & Community Development: Towards the Intelligent Society) and ICE-HUMS (Innovations for Sustainable Community Development: Research and Practices). We believe research and initiatives that has pragmatic and multidisciplinary/interdisciplinary approaches allows us to unravel fundamental problems and answer related questions regarding sustainable development.

The logistics of both of the First ICE-TES and ICE-HUMS 2021 conferences consist of two general and five-scientific keynote speakers. Special tracks are designed in each conference which cover recent developments in: ICE-TES (technologies, engineering, medical, and dentistry), ICE-HUMS (psychology, languages & cultures, economics, arts & design, and laws). The ICE-TES tracks received 82 submissions and 51 are accepted in the proceedings, involving authors from five countries, and corresponding to an acceptance rate of 62.2%. At the same time, the ICE-HUMS has received 130 submissions and 73 are accepted in the proceedings, involving authors from four countries, corresponding to an acceptance rate of 56.1%. All submitted papers were peer-reviewed on the basis of their significance, state-of-the-art contributions, and technical qualities.

Since we are still in the midst of COVID-19 pandemic, the conference has been organized virtually. The organizing committee has been working intensively to ensure that the scientific sessions will be valuable and engaging for all presenters and attendees. The parallel session format is a mix of pre-recorded and synchronous engagement through in-person live videos and question and answer sessions.

We would like to express our sincere appreciation to all the keynote speakers, committee members and reviewers for their dedication. Last, but certainly not least, we would like to offer many thanks to all authors who submitted their papers and all participants who registered to join this conference. We believe that ICE-TES and ICE-HUMS 2021 will be an inspiring academic occasion and will become a great platform for many ideas as well as research initiatives in the scientific community. Have an inspiring conference!

Dr. Hapnes Toba, M.Sc., General Chair of ICE-TES and ICE-HUMS 2021

Dr. Wahjoe Widowati, M.Si., General Co-chair of ICE-TES 2021

Joni, Ph.D., Ak., CA., CPSAK., General Co-chair of ICE-HUMS 2021

CONTENTS

PAPERS

FULL PAPERS











- What Is a Speech Chain and How Can This Concept Be Applied to the Various Areas of Speech Communication in an Intelligent Society? 5
Takayuki Arai
- Exploration of an Indonesian Currency Legality Detection System by Utilizing Image Intensity of RGB Mean Values 9
Ratnadewi Ratnadewi, Aan Darmawan Hangkawidjaja, Agus Prijono, Rudy Wawolumaja, Kartika Suhada, Maria Christine Sutandi, Andrew Sebastian Lehman, Elty Sarvia and Kervin Lusiano
- Comparative Study of Convolutional Neural Networks-based Algorithm for Fine-grained Car Recognition 18
Joseph Sanjaya, Mewati Ayub and Hapnes Toba
- Estimation of Paddy Leaf Nitrogen Status using a Single Sensor Multispectral Camera 26
Muliady Muliady, Tien Sze Lim, Voon Chet Koo and Nathaniel Pius Winata
- Taekwondo Poomsae-3 Movement Identification by using CNN 32
Novie Theresia Br. Pasaribu, Erwani Merry, Kalya Icasia, Jordan Eliezer, Che-Wei Lin and Febryan Setiawan
- Design and Implementation of a Path Finding Robot using Modified Trémaux Algorithm 39
Semuil Tjiharjadi
- Priority Petri Net Multimedia Model for Non-deterministic Events of Multimedia Presentations 49
Marvin Chandra Wijaya
- Anti-inflammatory Activities of Pineapple (*Ananas comosus*) Core Extract in Lipopolysaccharide-induced RAW264.7 Cell Line 58
Hanna Sari Widya Kusuma, Hartini Tiono, Philips Onggowidjaja, Selonan Susang Obeng, Wahyu Widowati, Cintani Dewi Wahyuni, Cahyaning Riski Wijayanti, Muhamad Aldi Maulana, Tri Handayani and Rizal Rizal
- Potential of Black Tea (*Camellia Sinensis* (L.) O. Kuntze) Extract as Anti-oxidant and Skin Anti-aging 65
Wahyu Widowati, Rita Tjokropranoto, Cindy Damayanti, Hanna Sari Widya Kusuma, Tri Handayani and Rizal Rizal
- Luteolin Possess Anti-inflammatory Effect on LPS Induced RAW 264,7 Cell Lines 74
Ervi Afifah, Hartini Tiono, Philips Onggowidjaja, Selonan Susang Obeng, Wahyu Widowati, Cintani Dewi Wahyuni, Cahyaning Riski Wijayanti, Muhammad Aldi Maulana, Tri Handayani and Rizal Rizal
- The Effect of Different Intensities of Treadmill Exercise on FGF23 Gene Expression in Gastrocnemius and Soleus Muscles of Wistar Rats 81
Julia Windi Gunadi, Diana Krisanti Jasaputra, Decky Gunawan, Ludovicus Edwinanto, Limdawati Kwee, Harijadi Pramono, Adrian Suhendra, Ghita Sariwidyantry, Hanna Goenawan and Ronny Lesmana

Antioxidant Properties of <i>Salacca zalacca</i> (Gaertn.) Voss Peel Ethanolic Extract Compared to Chlorogenic Acid <i>Ermi Girsang, Chrismis Novalinda Ginting, I Nyoman Ehrich Lister, Cahyaning Riski Wijayanti, Wahyu Widowati and Rizal Rizal</i>	87
Analyse Protein Model of the SARS-CoV-2 Virus using Data Mining Methods <i>Tiur Gantini and Hans Christian</i>	95
Antioxidant Properties of <i>Curcuma longa</i> L. and <i>Curcuma xanthorrhiza</i> Rhizomes <i>Dian Ratih Laksmiawati, Diah Kartika Pratami, Wahyu Widowati, Hanna Sari Widya Kusuma, Cahyaning Riski Wijayanti, Cintani Dewi Wahyuni, Ervi Afifah and Rizal Rizal</i>	104
The Effect of Agarwood Leaves Ethanol Extract on <i>Porphyromonas gingivalis</i> Growth Inhibition and in Vitro Cytotoxicity Assay on Fibroblast <i>Vinna Kurniawati Sugiaman, Henry Yonatan Mandalas, Ethan Yeshael Tanamal, Nathalia Cahya Calista and Natallia Pranata</i>	112
Comparison of Two Dental Age Estimation Methods: The London Atlas and the Schour & Massler Atlas in 3-23 Years Old Indonesian <i>Aprianisa Obsidiany Daisy Tarigan, Hendra Polii and Rosalina Intan Saputri</i>	122
The Effect of Apple Vinegar as an Irrigation Solution to Dental Root Canal Microstructure <i>Rudy Djuanda, Eliza Madyanty, Almira Anggarini Witjaksono, Vinna Kurniawati Sugiaman and Natallia Pranata</i>	126
The Color Dissimilarity based Method among Other Segmentation Methods: A Comparison <i>I Gede Made Karma, I Ketut Gede Darma Putra, Made Sudarma and Linawati</i>	131
Safety Driving Behaviour of Adolescents Pre-owning Driving License (SIM) <i>Sodikin and Hendramawat Aski Safarizki</i>	142
Virtual Reality Stimulants of Motor Ability through the Virtual Reality-based Game <i>Erwani Merry Sartika, Novie Theresia Br. Pasaribu, Richard Setiawan, Reynaldy Felicius Gunawan, Dion Melvern Siswanto, Che-Wei Lin and Febryan Setiawan</i>	146
Design of Bilateral Hand Movement Device using Design Thinking and Quality Function Deployment to Increase the Motoric Function of the Non-Dominant Hand <i>Novie Theresia Br. Pasaribu, Vivi Arisandhy, Christina, Elty Sarvia, Rainisa Maini Heryanto, Erwani Merry Sartika, Audyati Gany, Olga Catherina Pattipawaej, Richard Setiawan and Jessica</i>	153
Experimental Design of Driving with Distractions at Urban Area using Simulator Driving <i>Winda Halim, Rainisa Maini Heryanto, Santoso, Christina, Erwani Merry Sartika, Audyati Gany, Andrew Sebastian Lehman, Anggie Ervany Haryono and Vieri Candhya Wigayha</i>	159
Experimental Study on Velocity Profiles Due to Ecological Barriers <i>Robby Yussac Tallar and Teofilus Sawang</i>	167
Experimental Study on Riprap Layer Design for Circular Bridge Pier <i>Efferiki, Robby Yussac Tallar and Alexander Yovan Suwono</i>	172
Comparative Study of Riprap Model Design for Scour Protection of Bridge Pier <i>Cut Talitha Salsabila Nurapriili, Robby Yussac Tallar and Alexander Yovan Suwono</i>	176
The Experimental Study of Optimum Thickness on Riprap Layer Design <i>Dea Lidya, Robby Yussac Tallar and Alexander Yovan Suwono</i>	180

The Effect of Seismic Masses in Calculation of a 17 Multi-story Concrete Structure <i>Daud Rahmat Wiyono, Roi Milyardi, Yosafat Aji Pranata and Robby Y. Tallar</i>	184
Identification of Risk Factors for Delayed Time Schedule in Summarecon Serpong Playfield Preschool Project <i>Deni Setiawan and Stefanny Abigail</i>	190
Flood Risk Assessment of Heritage Building in Semarang City <i>Roi Milyardi, Deni Setiawan and Tri Octaviani Sihombing</i>	200
Identification of Risks in Making Decision for Overseas Expansion by Indonesian State-owned Construction Enterprise <i>Jeffrey Limas Lim, Ayomi Dita Rarasati and Mohammad Ichsan</i>	206
Pull-out Resistance of Glued-in Rod Embedded Parallel to Grain in Laminated Bamboo with Two Edge Distance Variations <i>Widiya Anistiya K. Rumasoreng, Karyadi and Nindyawati</i>	213
Experimental Study of Shear Strength of Purus Lobang Berkait (PLB): Masonry Wall <i>Marwahyudi, Senot Sangadji, Halwan Alfisa Saifullah and Stefanus Adi Kristiawan</i>	220
Engineering Education: Measuring the Relationship between Knowledge and Confidence to the Student Performance <i>Noek Sulandari, Cindrawaty Lesmana and Cindy Maria Setyana</i>	227
Bio-cord as an Ecotechnological Wastewater Treatment for Productive and Attractive Urban Open Spaces <i>Ferlina Sugata, Nathalia Yunita Sugiharto, Nina Nurviana, Seriwati Ginting, Isabella Ishipraya Andreas, Shirly Nathania Suhanjoyo, Andi A. Hamzah and Heddy Heryadi</i>	233
Relationship between Low Birth Weight (LBW), Birth Length, and Basic Immunization History with Stunting in Children Age 9 - 60 Months in Kabupaten Purwakarta <i>July Ivone, Stella T. Hasianna, Victor Yohanes S. and Vilia Ruthy W.</i>	245
Application of Freeze-thaw Harvest for SARS-CoV-2 PCR EQA Panel Material <i>Nur Ika Hariastuti, Nike Susanti, Hana Apsari Pawestri and Kartika Dewi Puspa</i>	250
Suicide and Narcissistic Personality Traits: A Review of Emerging Studies <i>Charissa Lazarus and Khamelia Malik</i>	254
Expected Attributes to Design Sleeping Facilities for the Elderly based on the Potential Stakeholders Point of View <i>Ely Sarvia, Elizabeth Wianto, Erwin Ardianto Halim and Elvira Natalia</i>	265
Wharton's Jelly Mesenchymal Stem Cells-secretedIDO as Candidate of Anti-inflammation Therapy <i>Wahyu Widowati, Teresa Liliana Wargasetia, Fanny Rahardja, Rimonta F. Gunanegara, Hanna Sari Widya Kusuma, Seila Arumwardana, Cintani Dewi Wahyuni, Cahyaning Riski Wijayanti, Tri Handayani and Rizal Rizal</i>	271
Factors Affecting Success of Team Members in Indonesia Scrum Implementation <i>Apriliana Fajri Wibowo and Yova Ruldeviyani</i>	279
The Application of Digital Module Design of East Sumba Woven Fabric on Interior Accessories <i>Erwin Ardianto Halim, Monica Hartanti, Maresha Caroline Wijanto, Yosepin Sri Ningsih, Hendra Setiawan, Yudita Royandi, Yunita Setyoningrum, Berti Alia Bahaduri and Aulia Wara Arimbi Putri</i>	286

The Use of Technology in Indonesian K-6 Education during Covid-19 Pandemic: A Review <i>Bayu Rima Aditya, Dina Fitria Murad, Oscar Karnalim, Aditya Permadi, Andrisyah, Fathul Jannah and Irawan Nurhas</i>	295
Build Software of Information Management Community Service Events <i>Febrina Anastasha and Teddy Marcus Zakaria</i>	305
User Interactions Analysis on a Moodle-based Online Learning Management System during Pandemic <i>Bernard Renaldy Suteja and Wilfridus Bambang Triadi Handaya</i>	314
Bioactivity of Soybean Tempeh against Diarrhea Associated Pathogen Is More Correlated with the Number of Total Bacteria than Specific Major Bacterial Phylum <i>T. E. Pramudito, E. G. A. Putri, E. Paluphi, G. Florencia, M. R. Gunawan, M. P. Pratiwi and Y. Yogiara</i>	320
Effects of Herbal Ingredients (<i>Allium sativum, Punica granatum, Curcuma longa, Curcuma xanthorrhiza</i>) on FATP3 Gene Expression in Aorta of High Fat Diet-fed Rats: A Preliminary Study <i>Diana Krisanti Jasaputra, Julia Windi Gunadi, Penny Setyawati Martioso, Larissa, Yenny Noor, Irna Permanasari Gani, Erik Dwikurnia Saiman, Desman Situmorang and Andi Haryanto</i>	328
Biochemical Characteristics of Ground Robusta Coffee under Various Postharvest Technologies and Processing Parameters <i>Sri Wulandari, Makhmudun Ainuri and Anggoro Cahyo Sukartiko</i>	333
Substantially Improved Antioxidant Activity of Modified Polymeric Nanostructure Entrapping Curcumin <i>Deni Rahmat, Wahyu Widowati, Etik Mardliyati, Eny Kusrini, Abdi Wira Septama, Yati Sumiyati, Mita Restinia, Sjaikhurrizal El Muttaqien, Cintani Dewi Wahyuni, Hanna Sari Widya Kusuma, Muhammad Aldi, Tri Handayani and Rizal Rizal</i>	344
Breast Cancer Histopathological Image Classification using Progressive Resizing Approach <i>Hendra Bunyamin, Hapnes Toba, Meyliana and Roro Wahyudianingsih</i>	351
Multi-Objective Bees Algorithm for Feature Selection <i>Natalia Hartono</i>	358
Eye Abnormality Automatic Detection using Deep Learning based Model <i>Audyati Gany, Meilan Jimmy Hasugian, Erwani Merry Sartika, Novie Theresia Br. Pasaribu and Hannah Georgina</i>	370
AUTHOR INDEX	377

The Effect of Different Intensities of Treadmill Exercise on FGF23 Gene Expression in Gastrocnemius and Soleus Muscles of Wistar Rats

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Keywords: FGF23, Treadmill Exercise, Gastrocnemius, Soleus.


Abstract: Fibroblast growth factor 23 (FGF23) acts as a hormone that regulates phosphate metabolism associated with kidney function, and an inducer of left ventricle hypertrophy. But the role of FGF23 as a myokine has not yet to be confirmed. This research aims to investigate the effect of different intensities of treadmill exercise on FGF23 gene expression in gastrocnemius and soleus muscles of Wistar rats. Twenty male Wistar rats were given different intensities of treadmill exercise (low, moderate, and high) for as long as 8 weeks. FGF23 gene expression in gastrocnemius and soleus muscles was examined using semi-quantitative PCR. In this study, we obtained no change of relative FGF23 mRNA expression in gastrocnemius muscles ($p = 0.684$) compared to control. But interestingly, we found a significant increase of relative FGF23 mRNA expression in soleus muscles ($p = 0.030$). These results showed that different intensities of treadmill exercise do not stimulate FGF23 gene expression in gastrocnemius muscles of Wistar rats. While the low intensity of treadmill exercise does not increase FGF23 relative mRNA expression, moderate and high intensities of treadmill exercise increase FGF23 gene expression in the Wistar rat's soleus muscles.


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1 INTRODUCTION

Fibroblast Growth Factor (FGF) could be divided into three categories: intracrine, paracrine, and endocrine (Kyrou, Weickert, Gharanei, Randeva, & Tan, 2017; Ornitz & Itoh, 2015). The FGF family consisted of 22 families, with FGF15/19 is being ortholog in rodents and humans, while FGF23 is included as an endocrine FGF (Ho & Bergwitz, 2021; Ornitz & Itoh, 2015). As a hormone produced in osteoblasts and osteocytes, FGF23 is circulated into many organs such as the kidney, heart, and skeletal muscles (Faul et al., 2011; López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013; Vervloet, 2019). The action of FGF23 is mediated by Fibroblast Growth Factor Receptor (FGFR) together with the cofactor Klotho (Ornitz & Itoh, 2015).

FGF23 is an osteokine (a hormone produced in bone), with the kidney as its main target, where it inhibits calcitriol formation by suppressing 25-hydroxyvitamin D-1 α -hydroxylase (Bacchetta et al., 2013; Ewendt, Feger, & Föllner, 2021). Recent researches have shown that FGF23 is also produced by cardiomyocytes (Leifheit-Nestler & Haffner, 2018) and induces left ventricular hypertrophy (Faul et al., 2011). These proofs ensuring the role of FGF23 in the crosstalk between bone and muscle (Ewendt et al., 2021; Lara-Castillo & Johnson, 2020). But it is still unclear whether FGF23 could directly alter skeletal muscle function. A study by Avin et al proved that FGF23 is indirectly influenced the proliferation and differentiation of skeletal muscle cells in an ex vivo experiment (Avin et al., 2018).

Many factors might alter molecular mechanisms in skeletal muscle, including the physiological adaptation process to different intensities of exercise (MacInnis & Gibala, 2017). Exercise has been well known as a way to reduce chronic disease risk (Anderson & Durstine, 2019). American College of Sports Medicine (ACSM) recommended light to moderate exercise that may progress gradually to vigorous exercise, 30 minutes/day and for a minimum of 3 days a week, for people without cardiovascular, metabolic, or renal disease (Riebe et al., 2015). Exercise induces numerous substances secretion, known as myokines which conduce positive effects to prevent metabolic disease and sarcopenia (Son, Chae, Testroet, Du, & Jun, 2018).

It is still unclear whether FGF23 is a myokine or just an osteokine induced by the change in phosphate concentration (Lara-Castillo & Johnson, 2020; Takashi & Fukumoto, 2020). Some studies

found increased serum levels of FGF23 after exercise in humans (Emrich, Dederer, et al., 2019; Kerschhan-Schindl et al., 2021; G Lombardi et al., 2014). While in mice, a previous study has shown that 1 week of treadmill exercise upregulated FGF23 in blood, mRNA expression, and mitochondrial function in skeletal muscle (Li, Fu, Zhao, Ni, & Shen, 2016). Therefore, in this study, we aim to investigate the effect of different intensities of treadmill exercise on gene expression of FGF23 in the Wistar rat's skeletal muscles (gastrocnemius and soleus).

2 METHODS (AND MATERIALS)

2.1 Experimental Animals

We obtained twenty male rats, Wistar strain, aged about 6-8 weeks, weight about 200-220 grams from PT Biofarma, Bandung, Indonesia. Rats were divided into four groups (N=5 for each group) and put in a cage per group under constant photoperiod (light/dark cycle every 12 hours), temperature between 22-24°, and relative humidity. Standard chow diet (47.3% carbohydrate, 4% fat, 20% protein, 12% water, 4% fiber, 12% calcium, and 0/7% phosphorus) and water were provided ad libitum. We experimented on animals based on the use and care of laboratory animal guidelines (Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research, Division on Earth and Life Studies, 2011). The rats were treated following an approved code of ethics from the Committee of the Faculty of Medicine, Maranatha Christian University- Immanuel Hospital Bandung Number 093/KEP/VI/2020.

2.2 Different Intensities of Treadmill Exercise

After two weeks of the adaptation period, the rats were trained to run on a treadmill with a gradual increase of speed and time for another two weeks for the initial adaptation. The protocol of treadmill exercise intensities was modified from the previous protocol, with lactate threshold as the basis for defining the intensities. The sub-lactate threshold is categorized as low intensity (10 meters per minute), lactate threshold as moderate intensity (20 meters per minute), and supra-lactate threshold as high intensity (30 meters per minute) (Lesmana et al., 2016). The treadmill exercise was conducted 5 times

a week, from Monday to Friday, 30 minutes per day, for 8 consecutive weeks. The sedentary group was used as a control group. At the end of the experiment, all the animals were sacrificed under inhalation anesthesia (5% isoflurane). We separated skeletal muscle tissues (gastrocnemius and soleus muscles), froze them at -80°C for RNA extraction.

2.3 RNA Extraction, Semi-quantitative PCR

RNA Trisure isolation reagent (Bioline, BIO-38032, London, UK) was used according to the protocol of RNA extraction from the manufacturer. After the extraction, RNA concentration and purity were quantified by measuring its absorbance in 260/280 nm (Tecan Infinite M200 Pro, No. 30050303, Switzerland). For the analysis of FGF23 and GAPDH gene expression, semi-quantitative PCR was conducted using a One-Step RT PCR Kit (Bioline, BIO-65409, London, UK). The process then continued with electrophoresis (Mupid Exu Submarine Electrophoresis System, Mupid Exu, Japan), and the result is visualized using Blupad Dual LED Blue/White Light Transilluminator (Bio-Helix, GeneDirex BP001CU, Taiwan). Quantification of the band was conducted using Image J. This procedure was adapted from the previous study (V. M. Tarawan et al., 2019). The primer sequences of FGF23 and GAPDH have been summarized in Table 1 (V. Tarawan, Gunadi, Subekti, Widowati, & Goenawan, 2019; Wang et al., 2017).

Table 1: Primer Sequence Used in This Study.

Gene	Primer Sequence		Product Size (bp)
	Upper strand: sense	Lower strand: antisense	
FGF23	CCTTCCTCTGCACTCGGTAG	TGCCAGCTGCCAAGACGGTG	301
	GTTACCAGGGCTGCCTTCTC	GATGGTGATGGGTTTCCCGT	

2.4 Statistical Analysis

Data are expressed as mean ± SEM. Differences between groups were evaluated by Analysis of Variance (ANOVA), followed by an LSD post hoc test. Statistical significance was set at p<0.05.

3 RESULTS AND DISCUSSION

As a result of this study, we found no difference in relative ratio of gastrocnemius’s FGF23 mRNA expression in different intensities of treadmill exercise were: 0.628 ± 0.05 (low); 0.593 ± 0.03 (moderate); 0.647 ± 0.02 (high); compared to 0.602 ± 0.04 (control). This result is presented in figure 1.

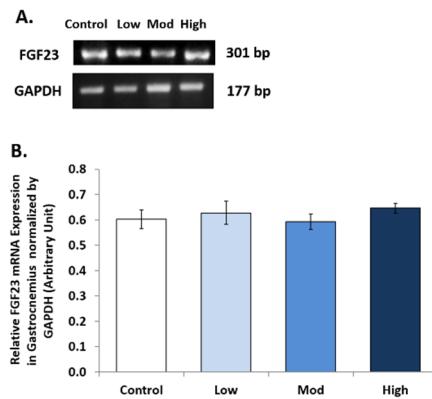


Figure 1: Relative Ratio of FGF23 mRNA Expression in Gastrocnemius Muscle of Wistar Rats After 8 weeks of Treadmill Exercise with Different Intensities. (Control = Sedentary, Low =low intensity (10 m/minute), Mod = moderate intensity (20 m/minute), High = high intensity (30 m/minute).

We found a significant increase of FGF23 mRNA expression in soleus muscles of Wistar rats ($p = 0.030$). Relative ratio of soleus’s FGF23 mRNA expression in different intensities of treadmill exercise were: 0.583 ± 0.06 (low); 0.624 ± 0.03 (moderate); 0.648 ± 0.05 (high); compared to 0.552 ± 0.02 (control). This result is presented in figure 2.

In this study, we found no difference of FGF23 in gastrocnemius muscle of Wistar rats after 8 weeks of treadmill exercise with different intensities. But interestingly, we found a significant increase of FGF23 gene expression in soleus muscles of Wistar rats after 8 weeks of treadmill exercise with moderate and high intensities, while low intensity did not change FGF23 gene expression compared to control.

Recent research has proven that the effect of FGF23 on skeletal muscles was mediated by other endogenous substances that might act in concert with FGF23 (Avin et al., 2018). Our result (figure 2) suggested the increase of FGF23 in soleus muscles might be associated with exercise alteration of skeletal muscle metabolism, particularly with parathyroid hormone (PTH). PTH and FGF23 are modulating each other’s secretion, FGF23 decreases

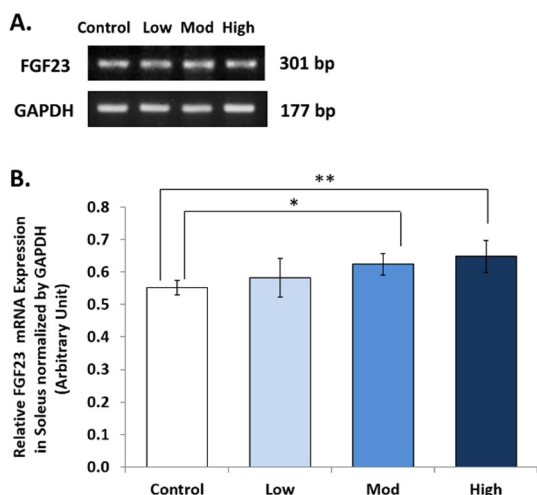


Figure 2: Relative Ratio of FGF23 mRNA Expression in Soleus Muscle of Wistar Rats After 8 weeks of Treadmill Exercise with Different Intensities. (Control = Sedentary, Low = low intensity (10 m/minute), Mod = moderate intensity (20 m/minute), High = high intensity (30 m/minute). * = significant ($p < 0.05$), ** = very significant ($p < 0.01$).

PTH secretion, and PTH increases FGF23 secretion (Giovanni Lombardi, Ziemann, Banfi, & Corbetta, 2020; Peacock, 2021). PTH responds to acute and chronic exercise, and its response might be influenced by some factors, such as VO_2 max, vitamin D status, and hormonal status (Giovanni Lombardi et al., 2020). A study by Gardinier et al proved that PTH has a role in bone adaptation to exercise, and they found an increase of FGF23 mRNA expression in the tibia after 6 days of treadmill training (Gardinier, Al-Omaishi, Morris, & Kohn, 2016). But the crosstalk between PTH and FGF23 in bone and skeletal muscles needs further investigation. Effects exerted by PTH in muscle cells might be secondary to the effects on other tissue. (Lombardi, Ziemann, Banfi, & Corbetta, 2020).

The different results between gastrocnemius (figure 1) and soleus muscles (figure 2) might be associated with different properties of their mitochondria. Gastrocnemius and soleus muscles are two muscles that differ in their fiber types, while gastrocnemius muscle is fast type muscle fiber, the soleus muscle is slow type muscle fiber (Qaisar, Bhaskaran, & Van Remmen, 2016). Soleus muscles have a slow contraction speed and predominantly use oxidative metabolism for energy production, while gastrocnemius is fast-twitch and uses glycolytic metabolism (Qaisar et al., 2016). Therefore, soleus muscles have more and bigger

mitochondria than gastrocnemius muscles (Sanchez, Li, Bragos, & Rutkove, 2014).

Different properties of gastrocnemius and soleus muscles could explain the different results of this study. A previous study concluded that exercise promotes FGF23 mRNA expression in skeletal muscle tissue by controlling mitochondrial function (Li et al., 2016). This is consistent with other studies that stated endurance training improved the function of muscle mitochondria which is essential for the homeostasis of energy in skeletal muscles (Zoladz, Koziel, Woyda-Ploszczyca, Celichowski, & Jarmuszkiewicz, 2016). These findings might explain why the increase of FGF23 was only found in soleus muscles (figure 2), but not in gastrocnemius muscles (figure 1).

The effect of FGF23 after exercise is still under debate because some studies have shown different results. Some studies claimed that FGF23 increased after exercise (Emrich, Dederer, et al., 2019; Kersch-Schindl et al., 2021; Li et al., 2016; G Lombardi et al., 2014), while other studies found no change/decrease ((Buskermolen et al., 2019; Emrich, Baier, et al., 2019; Keshavarzi, Daryanoosh, Kooshki Jahromi, & Mohammadi, 2017; Neves et al., 2021). Different results of those studies might be affected by intensities, duration, and type of exercise, high altitude, and phosphate intake. There is a possibility that FGF23 would increase more after a long duration, high intensity, over strenuous exercise, and high phosphorus diet. The limitation of this study is we have no data regarding phosphate and PTH concentration which might be correlated with the increase of FGF23 in soleus muscles. For a better understanding of the FGF23 mechanism in the adaptation of skeletal muscles to exercise, we recommend a more detailed study, especially by investigating the crosstalk between FGF23 and PTH, the function of skeletal muscles mitochondria after exercise, and longer duration of exercise.

4 CONCLUSIONS

In summary, FGF23 gene expression in gastrocnemius muscles is not upregulated after 8 weeks of treadmill exercise with different intensities but upregulated in soleus muscles after 8 weeks of treadmill exercise with moderate and high intensities. But the role of FGF23 in skeletal muscle after exercise still needs further investigation.

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