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ARTIKEL JURNAL INTERNASIONAL BEREPUTASI

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Nama Jurnal : Journal of Intelectual Disability Diagnosis and Treatment 2022
Penulis : **Agustini Utari**, Damianus Galih Panunggal , Tithasiri Audi Rahardjo , Wiwik Lestari , Ferdy Kurniawan Cayami , Tri Indah Winarni
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Bukti Konfirmasi Submit Artikel

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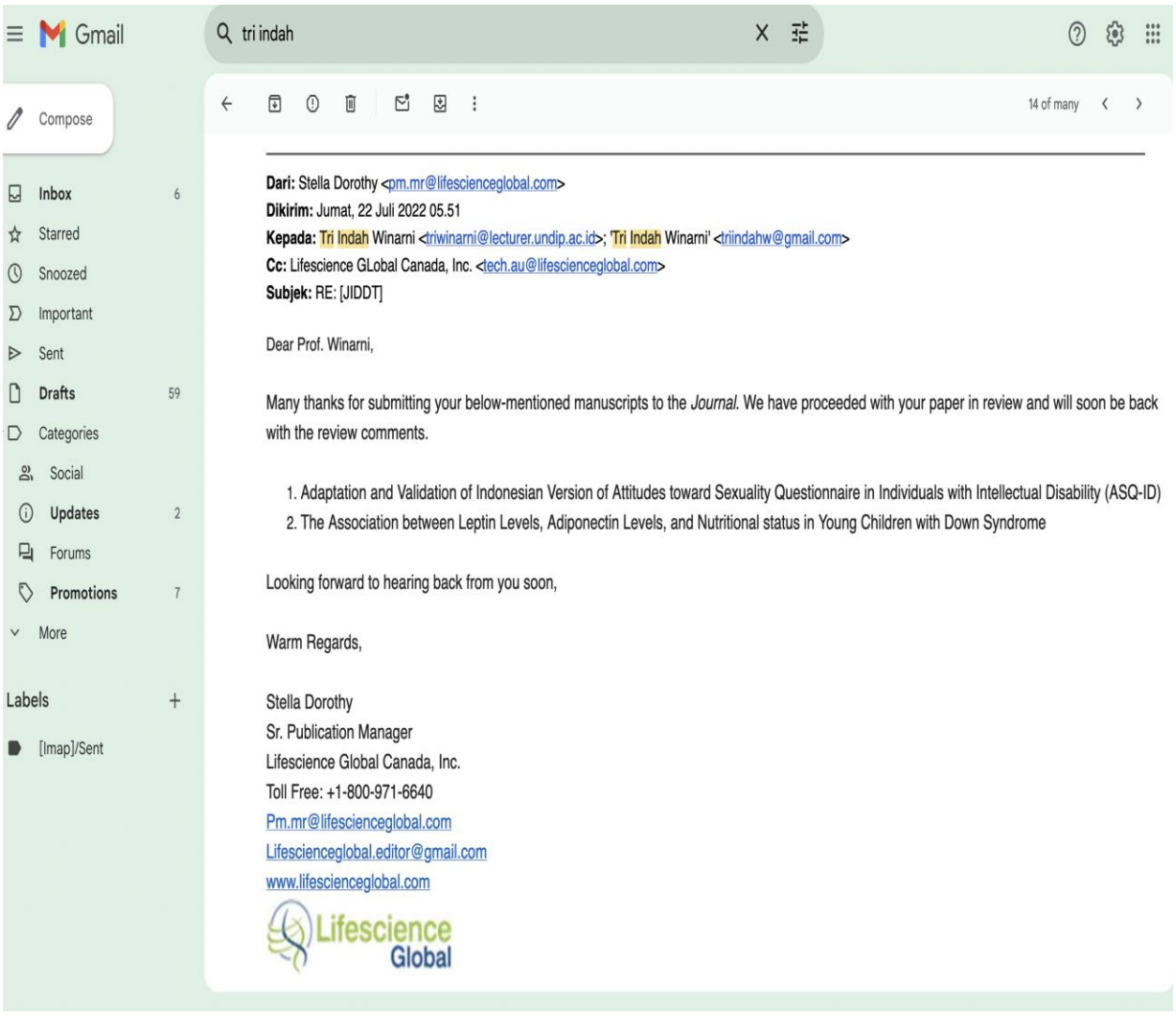

Dari: Stella Dorothy <pm.mr@lifescienceglobal.com>
Dikirim: Jumat, 22 Juli 2022 05.51
Kepada: Tri Indah Winarni <triwinarni@lecturer.undip.ac.id>; 'Tri Indah Winarni' <triindahw@gmail.com>
Cc: Lifescience GLobal Canada, Inc. <tech.au@lifescienceglobal.com>
Subjek: RE: [JIDDT]

Dear Prof. Winarni,

Many thanks for submitting your below-mentioned manuscripts to the *Journal*. We have proceeded with your paper in review and will soon be back with the review comments.

1. Adaptation and Validation of Indonesian Version of Attitudes toward Sexuality Questionnaire in Individuals with Intellectual Disability (ASQ-ID)
2. The Association between Leptin Levels, Adiponectin Levels, and Nutritional status in Young Children with Down Syndrome

Looking forward to hearing back from you soon,

Warm Regards,

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Trs: Manuscript entitled The Association between Leptin Levels, Adiponectin Levels, and Nutritional status in Young Children with Down Syndrome

Inbox

Tri Indah Winarni 10.14

to me

Follow up paper

Dari: Tri Indah Winarni
Dikirim: Jumat, 02 September 2022 13.34
Kepada: Stella <pm.mr@lifescienceglobal.com>
Subjek: Manuscript entitled The Association between Leptin Levels, Adiponectin Levels, and Nutritional status in Young Children with Down Syndrome

Dear Stella,
We are looking forwards for the reviewers comments of our second manuscript entitled
The Association between Leptin Levels, Adiponectin Levels, and Nutritional status in Young Children with Down Syndrome
Thanks
Best wishes,
Tri Indah Winarni, MD, PhD

Dari: pm.mr@lifescienceglobal.com <pm.mr@lifescienceglobal.com>
Dikirim: Kamis, 15 September 2022 03.21
Kepada: Tri Indah Winarni <triwinarni@lecturer.undip.ac.id>
Cc: Lifescience GLobal Canada, Inc. <tech.au@lifescienceglobal.com>
Subjek: JIDDT-Acceptance and Comments for Revision (Tri Indah Winarni 2)

Dear Prof. Tri Indah Winarni:

With reference to your manuscript entitled, **"The Association between Leptin Levels, Adiponectin Levels, and Nutritional status in Young Children with Down Syndrome"** submitted for publication in the **Journal of Intellectual Disability - Diagnosis and Treatment**, you will be pleased to know that your manuscript has been found suitable for publication after changes suggested by the referee (refer to the end of this email for Referee's Comments).

You are required to revise your manuscript according to the referee's comments. In addition to these comments, please check Editorial Requirements at **"Authors Guidelines"**, particularly in terms of the **reference section** when revising your manuscript. We greatly anticipate the submission of your revised manuscript (in **MS-Word**) as soon as possible. Kindly include a statement containing responses to 'Referee(s) Comments'.

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Best Regards,

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1. Referee Comments:

- 1-Title : **The Association between Leptin Levels, Adiponectin Levels, and Nutritional status in Young Children with Down Syndrome**
- There is no need to repeat "levels" twice

- 2- English language: some grammar mistakes need editing
- 3- **MATERIAL AND METHODS:**
- **Inclusion and exclusion criteria are lacking**
- **Were DS children with cong heart disease, hypothyroidism, or chronic illness excluded.**
- The authors should **include normal control children in the study**
- Sample size calculation **are lacking**
- **4-results**
- **Footnotes for tables are needed**
- If data were not normally distributed, quartile range is needed in addition to median, minimum and maximum values.
- Leptin was NOT correlated with HAZ, p-value=0.327. he author should correct this sentence
- 4-Discussion
- Studies (8,9): similarities and differences between these studies and the present study should described more clearly.

2. Referee Comments:

Thank you for the opportunity to review your manuscript. It was very interesting and provided a different perspective on commonly held beliefs. I would have found it helpful if you had provided definitions in text or a glossy for terms that are not used by lay people (like wasting). It would make your paper much more accessible. Thank you for undertaking this work.

Other comments:

1. Experimental methods, including statistics, are not adequately described
2. Writing style is not clear and with ambiguous statements.
3. Many Typographical and Grammatical errors

3. Referee Comments:

Thank you for the

· **English editing of the article is required**

· A higher concentration of leptin is found in overweight and obese individuals, among those populations, its receptor becomes resistant to leptin,[10] which,characterized by increased appetite, reduced satiety, over-consumption of nutrients, decreased metabolism, and increased total body mass.[11–13]

Rephrase this sentence.

· Therefore it could explain our finding that increased arm circumference can describe a higher fat mass, increasing leptin level in children with DS despite their non-obese nutritional status.

In CONCLUSION section, also state the correlation of Adiponectin levels with the nutritional status of study participants.

Perbaikan manuskrip (highlight kuning)

Original Research

The Association between Leptin, Adiponectin Levels, and Nutritional Status in Young Children with Down Syndrome

ABSTRACT

Background. Children with Down Syndrome (DS) have been associated with obesity. Leptin and adiponectin were also significant predictors of obesity and its comorbidity in DS. However, there was limited data regarding leptin and adiponectin in children with DS, particularly who were undernutrition. This study aimed to seek the role of leptin levels, adiponectin levels, and nutritional status in children with DS. **Methods.** This cross-sectional study was conducted on 40 children with DS aged 1 - 5 years. Height and weight were measured, and then the growth was interpreted using a DS growth chart. The Weight for Height Z-Score (WHZ) and Height for Age Z-Score (HAZ) were determined and Mid-Upper Arm Circumference (MUAC) was measured. Leptin and adiponectin serum were analyzed using the enzyme-linked immunosorbent assay (ELISA) method. Mann-Whitney test was done to compare leptin and adiponectin levels in normal and wasted groups, while Spearman's analysis was carried out to correlate between laboratory results and anthropometric parameters. **Results**. Forty children were participated (23 males, 17 female) with a median age was 25.5 months. Ten out of 40 children with DS (25%) were wasted and leptin was significantly lower in wasted compared to normal children, in addition, leptin was significantly correlated with WHZ ($r = 0.415$; $p = 0.008$), and MUAC ($r = 0.427$; $p = 0.006$). While, adiponectin did not significantly correlate with those anthropometric variables in both wasted and non-wasted groups. **Conclusion**. Leptin associates with WHZ and MUAC and it decreases in wasted children with DS.

Keywords: adiponectin, Down syndrome, leptin, nutritional status, wasted, young children

1. INTRODUCTION

Down Syndrome (DS) is a genetic abnormality that CDC predicts occurs in 1 baby in every 691 babies born in the USA. Children who are born with DS have associated comorbidities such as congenital heart defects, hypotonia, feeding and swallowing difficulties, hypothyroidism, and an increased risk of recurrent infection and autoimmune disorders.[1,2] Compared to typical children, DS children tend to have a short stature, small head circumference, and higher Body Mass Index (BMI). Around 23% - 70% of children and adolescents with DS are overweight or obese.[3,4] However, due to congenital heart defects, oral motor difficulties, and pharyngeal dysphagia, younger children with DS would develop a condition of failure to thrive in early life.[2,5,6] A retrospective study of obesity in children with DS also reported BMI Z-scores significantly increased in those over 12 years old, and age did not significantly associate with BMI Z-scores in DS children ages 2-7.[7]

In previous studies, leptin was significantly higher, while adiponectin was significantly lower in children with DS compared to typical non-obese children.[8,9] Leptin and adiponectin are two biochemical compounds produced by fat cells in white adipose tissue, and they are associated with metabolic syndrome, more specifically, obesity and insulin resistance. A higher concentration of leptin is found in overweight and obese individuals. Among those populations, its receptor becomes resistant to leptin,[10] which is characterized by increased appetite, reduced satiety, over-consumption of nutrients, decreased metabolism, and increased total body mass.[11–13] Higher adiponectin is associated with higher insulin sensitivity.[14] Adiponectin improves energy homeostasis by increasing fatty acid oxidation and glucose utilization on skeletal muscle and inhibiting gluconeogenesis on the liver. Adiponectin also acts as an anti-inflammatory agent which protects the heart, lungs, vascular system, and colon.[15] In malnourished children, serum leptin was lower than those in normal-weight children, because of losing adipose tissue.[16] Low leptin levels would disturb the metabolic, endocrine, and immune system.[17] Several factors could interfere with leptin concentration, such as glucose, estrogens, inflammatory cytokines, thyroid hormones, and androgens.[18] A previous study concluded that leptin is not only affected by fat mass. It is also affected by reproductive hormones, as the study found higher leptin in adolescents with rapid weight gain during their 0-18 months of life.[19]

Although some studies mentioned the involvement of leptin and adiponectin in older children and adolescents with DS, there are limited data and descriptions on these hormones in younger malnourished children with DS. Therefore, this study aimed to determine the correlation between leptin and adiponectin levels and nutritional status in young children with DS.

2. MATERIAL AND METHODS

2.1 Study Design & Participants

A cross-sectional study with a consecutive sampling method was conducted on 40 children with DS. A correlation sample size calculation was applied using the alpha and beta of 0.20, with the reference r value 0,335, and the result of minimum sample value is 39 children[20]. The inclusion criteria were children aged 1 – 5 years old who were clinically diagnosed with DS by an

an experienced pediatrician (AU) from three hospitals in Central Java Province (Dr. Kariadi Hospital, Semarang; Diponegoro National Hospital, Semarang and R. Soedjati Soemodiardjo Hospital, Purwodadi). Children who have severe acute illnesses were excluded. This study was approved by the Ethical Committee (No.100/EC/KEPK/FK-UNDIP/VI/2020), and written consent was obtained from parents or caregivers prior to the study.

2.2 Research Procedure

Demographic characteristics, history taking, and physical examination were done by an experienced pediatrician in managing Down Syndrome (AU). Body length/ height was measured using SECA 417 infantometer for children below two years and SECA 213 stadiometer for children aged two years and older. Body weight was measured using AND UC-322 weight scale, and mid-upper arm circumference (MUAC) was also measured. Anthropometric data was then calculated, including Weight for Height Z Score (WHZ) and Height for Age Z-score (HAZ), using the Peditools calculator for children with Down Syndrome [3] (accessible on https://peditools.org/downpedi/) to assess nutritional and growth status. The nutritional status was divided according to the WHZ cut-off. MUAC was compared using the cut-off point of 13.5 cm. (see **table 1**).[21] For variable analysis, the WHZ classification of nutritional status was simplified into two categories (WHZ -2 or higher considered normal weight (normoweight) and below -2 SD considered wasted).

2.3 Leptin and Adiponectin Assay

Peripheral blood vein was obtained in the morning from all participants before the first meal. Three mL of blood vein was collected and then centrifuged with 1000 G force for 15 minutes. The serum was then aliquoted and stored at -20^{o}C temperature before assay. Leptin and adiponectin levels were measured from the blood's serum using Enzyme-Linked Immunosorbent Assay (ELISA) by DRG® Leptin Sandwich ELISA for Leptin and Quantikine® ELISA for Adiponectin. All the laboratory procedures were done at GAKI laboratory, Faculty of Medicine, Diponegoro University, Semarang.

2.4 Statistical Analysis

Data were analyzed using SPSS version 25 (SPSS, Chicago, IL). The Shapiro-Wilk normality test was used to determine the data distribution. As we found that our data were not normally distributed, we provided our data in the median, minimum-maximum values, and interquartile range. A comparison between nutritional status and laboratory data was carried out using Mann-Whitney's analysis. The correlation between leptin and adiponectin was calculated, and thus, between laboratory parameters and WHZ, HAZ, and MUAC. All correlations analyses were done using Spearman's rho non-parametric analysis. Statistical significance was defined as p values < 0.05.

3. RESULT

A total of 40 children with DS were included in this study (23 males, 17 females), with a median age was 25.5 months (12 – 56). Most of the participants (75%) were normoweight, and only ten children (25%) were wasted (WHZ < -2 SD). (see **Table 2**) Leptin concentration varied between

4. DISCUSSION

In this study, 25% of the participant was classified as wasted, one of the malnutrition parameters. No DS children were found with overweight or obese. This finding is different from previous studies, as most of them found that children or adults with DS had a more significant risk of being overnourished.[3,8] Children with DS were more likely to become obese as they grew, and studies regarding obesity in children with DS involved children and adolescents of a wide range of ages, so the young age of our patients may be a contributing factor. However, in DS, hypotonia can lead to feeding and swallowing problems, such as masticatory dysfunction and aspiration. These will eventually hinder nutritional intake.[5,22]

In our study, despite non-overweight nutritional status, leptin was still positively correlated with WHZ. Leptin level was also higher in normoweight children, compared with underweight children. This finding was similar to another study that found significantly lower leptin levels in malnourished children.[16] Leptin was widely known to correlate with adiposity, increased appetite, and obesity.[5,9,10] In children with DS, leptin was also correlated with obesity and lipid profiles. A previous study also found a higher concentration of Leptin in children with DS than in their siblings [9]. Our study did not compare DS with the control group. However, we also found the median leptin value in children in normoweight DS children was 2.01 ng/mL, which this value was similar to the study from Tenneti et al who found the mean leptin value in DS children was 2.0 ng/mL.[8]The exact mechanism of increased leptin in normoweight children with DS is not yet known, but it may be caused by the genetic defect children with DS have.[12] Another study in Oregon stated an increasing rate of overweight and obesity in children with DS as children get older.[23] This finding can explain our findings regarding the significant correlation in leptin with BMI/Weight for Height despite the children being normoweight or undernourished. However, it should be consider that low leptin levels could affect the secretion of growth hormones and growth factors, leading to growth retardation.[24,25] Leptin deficiency will also affect bone growth. A study in the mice model suggested a significant inhibition of chondrogenesis in the tibial plate in leptin-deficient mice.[26] In contrast, the same study also found that vertebral chondrogenesis was not inhibited by leptin deficiency. However, this would still decrease total bone mass, as appendicular bones contribute 80% of total bone mass.[27]

Our study found a positive correlation between leptin level and arm circumference. As one of the primary anthropometric measurements done routinely, arm circumference correlates to higher BMI and obesity.[14,15] Furthermore, arm circumference has been used as one variable for predicting weight in children. The measurement of arm circumference and humeral length used in Mercy TAPE is the most accurate way to predict the children's weight, with no exception for children with Down Syndrome.[17,28] MUAC has also been used as a useful screening tool for diagnosing malnutrition, particularly in the community. Moreover, a study found that MUAC > 12.5 cm had high sensitivity and specificity for diagnosing malnutrition and monitoring its treatment.[29] A study also explains that a component of MUAC measurement, specifically Total Arm Area (TAA), significantly correlated with BMI, as both represent body fat composition. They also mentioned that MUAC was better at diagnosing chronic malnutrition when compared to BMI.[30] Those studies support our finding that increased arm circumference refers to a higher fat mass, which might also increase leptin levels in children with DS despite their non-obese status.

In contrast with leptin, obesity and metabolic syndrome are associated with a low adiponectin level. Conversely, a study found that adolescents with DS have a significantly lower adiponectin level than the control group. They also found that adiponectin levels in DS tend to increase during adulthood, serving as a cardioprotective agent.[31] A previous study in Northwest India found lower adiponectin levels in children with DS compared to healthy children, although not statistically significant. They also reported that there is no correlation between adiponectin with BMI in DS and control groups[8]. It is similar to our study, which showed that adiponectin level was not significantly correlated with BMI-Age Z-Score. In another research studying older children with peritoneal dialysis, adiponectin was higher than in children without renal disease. This finding was in line with the lower BMI in the study group. The researcher suggested that the catabolic state of renal failure triggered adiponectin release to increase insulin sensitivity and energy expenditure.[32] In this study, although we found malnourished children, we did not find any severely malnourished children. It may explain our insignificant negative correlation between adiponectin and body composition parameters.

This study had some limitations. We did not thoroughly measure the body composition, especially fat body composition, as leptin and adiponectin are adipokine and should be correlated with body fat. We also did not measure insulin and insulin resistance, as those two variables could better explain the adipocytokines measured in our study. Finally, this study did not exclude patients with hypothyroidism, congenital heart defect and other chronic illnesses, those may affect leptin and adiponectin levels.

5. CONCLUSION

In conclusion, there is a difference in leptin levels among wasted and normoweight children with DS, but not adiponectin. In addition, Leptin correlates with WHZ and MUAC but not HAZ, while adiponectin is not correlated with WHZ, MUAC, and HAZ. Future study is needed to consider detailed body composition measurements such as body fat mass, fat-free mass, visceral fat mass, and skeletal body mass using the dual X-Ray absorptiometry (DXA) method[33]; thus the correlation between leptin and fat composition in children with Down Syndrome can be better analyzed.

>>> On Thu, Oct 27, 2022 at 11:29 AM Farrukh Imran
>>> <fimran@lifescienceglobal.com>
>>> wrote:
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>>>>
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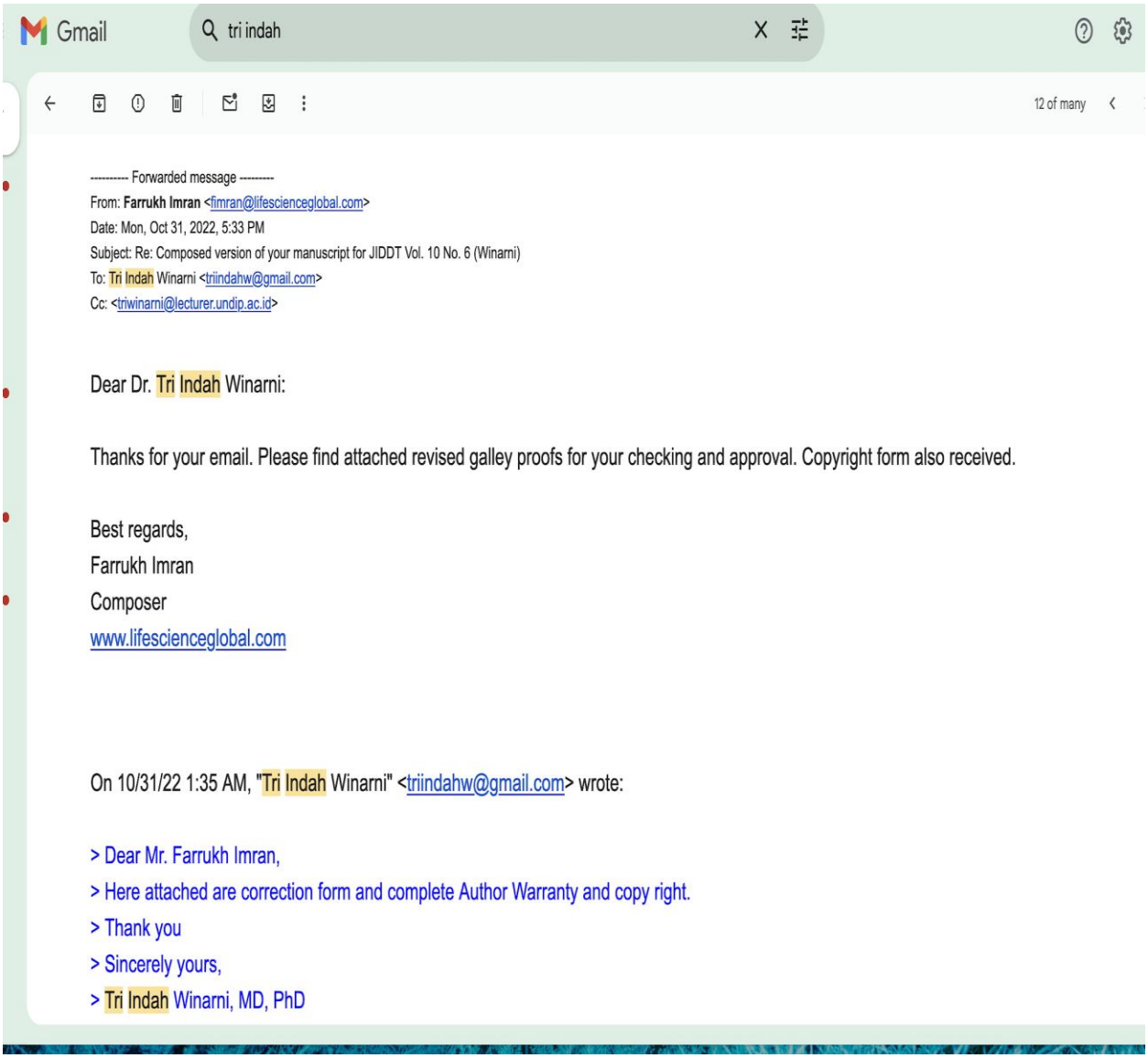
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