Bachelor's project

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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Muscle function and menopausal women

- Hormones, physical activity and vitamin D.

BEV2900 - Spring 2021

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Abstract.

English: **Purpose:** To investigate how the effect of hormones (estrogen deficiency) in menopausal women affects grade of muscle function and differentiating that from normal aging of muscle function and sarcopenia. **Method:** A systematic review that included nine peer reviewed studies found through Oria. Inclusion criteria was it had to conduct at least one of the menopausal stages, aged 40 to 70 years, and the following keywords below. **Result:** Hormones do affect muscle function and that hormone therapy combined with physical activity (preferably exercise) is beneficial to maintain normal muscle function, and sometimes even increase muscle performance. **Conclusion:** Hormone therapy and physical activity/exercise are the best treatment for menopausal women to maintain muscle function. Before starting up any hormone treatment and exercise program, it is recommended to consult with a physician.

Norwegian: **Formål:** Undersøke hvordan effekten av hormoner østrogen mangel påvirker grader av muskelfunksjonen hos kvinner i overgangsalderen, sett bort fra normal aldring av muskelfunksjonen og sarkopeni. **Metode:** Systematisk gjennomgang av ni fagfellevurderte studier funnet i Oria søkeportalen. Inkluderings kriterier var minimum en av fasene i overgangsalderen, alder 40-70 år, og følgende søkeord (keywords) nedenfor. **Resultat:** Studien tilsier at hormoner påvirker muskel funksjon, hormon terapi kombinert med fysisk aktivitet (foretrukket trening) er gunstig for å opprettholde en normal muskelfunksjon og noen ganger forbedre muskulær ytelse. **Konklusjon:** Hormonterapi og fysisk aktivitet/trening er en gunstig behandlingsform i opprettholdelse av muskel funksjoner hos kvinner i overgangsalderen. Før oppstart av hormonterapi og treningsprogram, er det anbefalt å konsultere med en lege.

Keywords. estrogen, menopause, postmenopause, premenopause, perimenopause, ageing, muscle function, hormone and women.

Introduction.

This bachelor assignment in movement science, has as theme muscle function and aging. A lot of what's happening to a woman's body is in the menopause and can make changes in the hormones, and it can affect both physically and mentally. Menopause is divided into three stages: perimenopause, pre-menopause and postmenopause. The first stage is perimenopause and it is when the menstrual cycle is irregular, and may start to experience some symptoms like hot flushes (vasomotor dysfunction). This stage can start as early as the age of 30`s, but more common in the age between 40-50 years. The pre- menopause stage is when the menstrual cycles stop because of the lack of secretion of the ovarian hormones, estrogen and progesterone. Symptoms may increase in this stage; Vasomotor dysfunction and vaginal dryness are consistently associated with menopause. Other symptoms are anxiety, depression, mood changes, sleep disturbance/insomnia, cognitive changes and somatic complaints. (Nelson, 2008) Another article mentions decreased libido, fatigue, joint and muscle pain. Sexual dysfunction, and urinary incontinence have mixed data for efficacy of estrogen treatment and menopause, or if it is an aging process. (Nanette, et al., 2015)
After the age of 55 years, it is common to say they are in the postmenopausal stage as long they have been 12 months amenorrhea. Even though the menopause is a normal event for women, the individual experiences vary.

When we are aging, the body's muscle mass reduces, and can lead to impaired muscle strength. Simultaneous muscle mass reduces the storage of fat and connective tissues in the skeletal muscle. Factors like hormonal changes and changed protein synthesis can lead to changes in activity abilities, muscle mass and function. According to a study by Greising (2009) women lose their muscle strength by approximately 1% per year after premenopause, and at a higher rate past 70yrs. (Greising, 2009) Since hormone production reduces in the menopause, many women use hormone therapy (HT) to relieve symptoms, it replaces the hormones. HT can also prevent osteoporosis, which is more common after menopause. The benefits of using HT usually outweighs the risks for most women, but the risks are usually small and depend on the type of HT, how long you use it and your own health. The risks can be breast cancer, blood clots, heart diseases and stroke.

The female sexhormone (estrogen) consists of substances; estron, estradiol, and estriol. Estriol is produced in the placenta from estradiol. Estron is a substance development from

androstenedione (androgen steroide hormone) for estradiol, takes over for estrogen in the postmenopausal stage. Androstenedione does not increase muscle mass, but serves as a bi-product and increases growth hormone production during puberty (amongst other hormones). Non pregnant women produce estrogens (follicle hormones) in their ovaries, this secretion slows down in the pre-, peri- and postmenopausal stages.

Hypothalamus is the head of coordinating hormonal activities in the autonomic nervous system and the endocrine system. Hormones are chemical messengers that regulate the process of hormone secretion to the targeted cells. These cells have receptors that bind to specific hormones. Neurohormones are produced by nervous cells in the Hypothalamus, and are often called neuroendocrine cells, transported by fluids such as blood throughout the body. Endocrine cells receive information from the targeted cells, called “Feedback control”. The most common form is “Negative Feedback control”, here the endocrine cells register a shift in target-cells activity and from there they implement a counteraction of that activity. The “Feedback control” is an important regulator of the body's own homeostasis (internal environment). It is a fine adjustment where the target cells run the endocrine cells hormonal secretion, by giving a message to either increase or decrease the endocrine cells stimuli on the targeted cells. If Episodic secretion stops it will lead to irregular menstruation, secretion becomes rarer even if levels of Luteinisating hormone and Follical stimulating hormones stay unchanged. The largest amount of cells in the pituitary anterior lobe are growth hormone producing cells, and the secretion is highest at night. Hypothalamus produces the growth hormone-releasing hormone and the growth hormone- inhibiting hormone. Physical work, fasting, stress, low glucose concentration, and protein rich meals can result in an increased growth hormone-secretion. Cortisol can also inhibit the growth hormone-secretion. Growth hormone stimulates the uptake of amino acids and increases the protein synthesis, both leading to an increased muscle mass. This is because of the increased number of cells (hyperplasia) and the size of the cells (Hypertrophy). Making the growth hormone an anabolic hormone, it also stimulates the fat-decomposition, fatty acids and glycerol from fat-tissue to the blood, Acetate binds to CoA-(Coenzyme Acetate) leading to acetyl-CoA, Crebs cycle in the matrix of the mitochondria.

The pituitary anterior lobe produces six hormones; Thyroidea stimulating hormone, Adrenocorticotropt hormone, follical stimulating hormon, Luteinisating hormone and growth hormone are all Trophical hormones. Somatotropt hormone stimulates the production of gender hormones, regulating growth and maturity of gendercells, and lastly the non trophical hormone Prolaktin. The pituitary anterior lobe is the superior endocrine gland, producing hormones that regulate hormonal production in other endocrine glands; the thyroidea, adrenal glands and the gonads. If Episodic secretion stops it will lead to irregular menstruation, and secretion becomes rarer even if levels of Luteinisating hormone and follical stimulating hormones stay unchanged.

Vitamin D, a common name for a group of steroid hormones, vitamin D3 in mammals and Vitamin D2 produced in plants. Vitamin D3 is not biologically active, but reacts with hormones and is the body's way of storing Vitamin D, activated by enzymes in the liver forming calcidiol (25- (OH)2- vitamin D3), and then produced in the kidneys. This is a “Negative feedback control” which prevents an overconsumption of the body's Vitamin D store. Vitamin D3 is a prohormone found in the skin tissue from (Ultraviolet B rays) and converts dehydrocholesterol into pre-vitaminD3, a conversion of cholesterol catalyzed by enzymes. These steroid hormones cannot be stored in vesicles. That is why secretion and cell hormone production continuously adapt to the needs of the body, and hormone production-speed will determine the hormone secretion-speed. Vitamin D3 metabolites, steroid hormones and thyroidea hormone are fat soluble (hydrophobic) bound to transport-protein in the blood. The hormones have something called plasma half-life (storage time) which lasts from hours to days. Maintaining stability and regulating target cells function, mobilizing and releasing the necessary amount of hormones, as the free concentration in the blood decreases, keeping it stabile.

The Risk of having too little of vitamin D, is associated with the immune system's inability to prevent infections, muscle weakness, fatigue, diabetes, cancer, depression, multiple sclerosis, high blood pressure, heart diseases, stroke and osteoporosis. Vitamin D insufficiency and hyperparathyroidism have been associated with reduced muscle strength, physical performance, postural stability, well-being, and quality of life. Hypercalcaemia (too much vitamin D) have the risks of depression, muscle weakness, confusion, headache, nausea/vomiting, frequently urinating and thirst. (Bisley, 2018)

Based on common knowledge about hormonal changes (estrogen levels) in menopausal women and how they affect the female body, this study assumes that it influences muscle function. Vitamin D and hormone secretion are affecting the hormonal balance and muscle function, this being in a menopausal transition or not, and it can affect how menopause symptoms are being treated. It is important to look into how hormones affect muscle function in menopausal women because it can change the treatment in different menopausal stages and how to manage their symptoms, quality of life and muscle function later. The main question is how the effect of hormones (estrogen deficiency) in menopausal women affects grade of muscle function, and differentiating that from normal aging of muscle function and sarcopenia.

Method.

The method of this study is a systematic review, studies were chosen from database Oria, date. 29.th of April. Articles that we found in Oria were rarely available online there, we found the article online using google scholar. Following Keywords were used in Oria.no with combinations of "and/or"; estrogen, deficiency, menopause, postmenopause, premenopause, perimenopause, ageing, muscle function, sarcopenia, hormone, women and vitamin D. Then each search was sorted by relevance "peer-reviewed". In search engine Oria, you can narrow down search by excluding and inclusion criteria's, and after that it showed 2927 articles related to the topic. Eight articles were chosen, and one other article was found through another article's references**.** Criteria's included was that it had to be in English or Norwegian and conducted on humans. Every article had to include some of the keywords mentioned above, and had to include at least one of the menopausal stages. Age had to be around the same in every article, there are some differences and that is because of the menopausal stage that the studies are investigating. To measure muscle function our criteria is that some of the measurements had to be the same, so it is possible to compare them.

Results.

Nine studies were included in this study with a total of 1509 persons. We have separated the different articles, first comes the ones which include training with menopause, then adding HT and at last vitamin D.

1. Bemben (2000) included 25 postmenopausal women aged 41-60 years in their randomized - control study. Intervention group received high-load and high-repetition training (N = 17), and the control group had no training (N = 8). The results found that there were no significant differences between the groups for the baseline values in the 12 strength training exercises. Only the high-load group showed a significant increase in shoulder press, quadriceps and hip flexion strength. None of the training groups showed a significant improvement in biceps curl, triceps extension or hip abduction, and for the control group biceps strength significantly declined. The high-load and high-repetition groups had a greater increase for Latissimus pull, seated row, leg press, hip extension, hamstrings, hip flexion and hip adduction exercises; they showed significant group differences in percent changes in strength than, compared to strength in the control group. The overall percent changes in muscular strength was 30 % for the high-load group, 27% high-repetition group, compared with -3% for the control group. Both of the training groups showed similar improvements in the lower body (high-load 30%, high-repetition 30%, control -3%), hip strength had better improvement in the high-repetition group (high-load 37%, high-repetition 40%, control -1%). For upper body strength, high-load had greater improvement by 25 % versus high-repetition with 16%, and lastly control group decreased by -6%. The conclusion is that both the high-load and high-repetition resistance training were effective in improving muscular strength in postmenopausal women. (Bemben, 2000)
2. Bondarev (2018) included 813 pre- (N = 233), peri- (N = 281) and postmenopausal (N = 299) women aged 47-55 years in their cross-sectional study. Where physical activity was self-reported and got tested in knee extension, handgrip, jump height, maximal walking speed and 6min. walking. Their results showed that women who trained on a regular basis, performed with better results in the hand-grips strength test, maximal knee extension and 6-min. walking. They also showed that there is no significant interaction between the menopausal stage and physical activity in muscle performance. Their results also show that postmenopausal women had greatly weaker hand-grip strength than the premenopausal group, and the perimenopausal is in no significance to the two other groups. In all of the tests except from the 6 min. walking test showed that there is a decrease in muscle function in every menopausal stage. Even though women with higher physical activity in peri- and postmeopausal, showed a greater performance in lower body muscle power, then those with lower physical activity. Although women in postmenopausal were reporting about functional

limitations in daily activities. The main conclusion was that menopause status is associated with muscle strength and power, but with mobility/walking it is clearly weaker. A high physical activity level provides more capacity to counteract the potential negative influence of menopausal factors on muscle function. (Bondarev, 2018)

3. Bemben and Langdon (2001) included 40 postmenopausal women aged 53-65 years in their cross-sectional study. Intervention group (N = 20) received estrogen therapy and the control group (N = 20) had no estrogen therapy, 1-RM cybex isotonic weight machines were used to measure muscles. Their results showed that there were no significant differences in the muscle strength between estrogen therapy and non-estrogen therapy, even though they adjusted for body weight and lean body mass. The conclusion in this study is that women who are taking Estrogen have similar muscular strength, size and body composition, as those lacking estrogen. (Bemben & Langdon, 2002)

4. Ronkaine (2009) included 15 twins aged 54-62 years, where each pair had one that used HT and the other non-HT. This is a co-twin control study and tested for knee extension, handgrip, jump height, habitual and maximal walking speed 10m. They found that the maximal walking speed of HT group was 7% greater compared with non-HT group (2.2 m/s and 2.0 m/s,). When it came to habitual walking speed, they could not differ between HT group and non-HT group. In muscle strength they found that in the lower body strength HT group had 16% greater muscle strength than their co-twins. This difference was clearly done to better muscle power among HT group, in the vertical jump test they could elevate their body 21% higher than their twin with non-HT. Although maximal isometric strength test between HT group and non-HT group had no significant differences between the groups. The conclusion in this study is that HT group was associated with better mobility and greater muscle power among the 54-62 years old women. (Ronkainen, 2009)

5. Taaffe (2005) studied the effect HT and/or exercise on skeletal muscle attenuations in postmenopause. They included 51 postmenopausal women aged 50-57 years in their randomized, double-blind control study. They were divided into four groups; exercise

group (N = 12) and exercise + HT (N = 10) received high impact training, HT group (N = 14) and control group (N = 15) had no training. Measurements used were cross-sectional area of quadriceps and posterior muscles, knee extension, jump height and running speed 20m. Their result showed that there was an increase in cross-sectional area in quadriceps for HT group and exercise + HT group, compared with the group for only exercise and control. Comparing the HT group with control group and exercise + HT group compared with exercise group, they found an increased strength of the posterior muscles. For muscle performance there was no significant interaction for knee extensor, but for jump height and running speed 20m. increased in the HT group and exercise + HT group compared with control group. Even though the effects are modest, the results indicate that HT alone or combined with exercise, may improve/preserve skeletal muscle attenuation in postmenopause, and exert a positive effect on muscle function. They don't have a clear conclusion, but their findings in the results are open for discussion and further investigation. (Taaffe, 2005)

6. Finni (2011) investigated if muscle function in 13 monozygotic postmenopausal female twins aged 54-62 years discordant for HT. This is a co-twin control study where each pair had one that received HT and the other non-HT. They measured maximal voluntary torque and twitch characteristics - electrical stimulation. The results of this study are that twitch torque was 32% higher in HT group than the non-HT group. Maximal voluntary torque did not differ between the groups, neither in the activation level or twitch time. Mean level of voluntary activation in HT group was 11% from the full capacity of force production, compared with 15% in the non-HT group. They also tested for fatigue and the results say that HT group fatigued more than the non-HT group. Conclusion in this study is that in early postmenopausal women using HT the involuntary mechanisms of the plantar flexors amplifies, but not for the voluntary. (Finni, 2011)

7. Cangussu (2016) included 160 postmenopausal women aged 50-65 years in their randomized, double-blind, placebo-controlled trial. Intervention group (N = 80) received vitamin D supplementation and the control group (N = 80) received placebo. Measurements used in this study are handgrip and chair rising. The results showed that after the 9 months intervention the average values of vitamin D increased from 15 to 27.5 ng/ml in the Vitamin D supplementation group, and as assumed decreased in the

placebo group from 17 to 14 ng/ml. The Vitamin D supplementation group had a significant increase in muscle strength of the lower limbs by chair rising test, in the placebo group there was considerable loss in the lean mass. The conclusion in Cangussu`s study was that Vitamin D supplementation in postmenopausal women permitting an important increase in muscle strength and control of the progressive loss of lean mass. (Cangussu, 2016)

8. Bisley (2018) included 81 postmenopausal women aged 60-80 years in their randomized, placebo control trial. Intervention group (N = 40) received a high dose of Vitamin D supplementation and the control group (N = 41) received a placebo. Muscle strength was measured by maximal voluntary isometric muscle strength and maximum force production at handgrip, upper and lower extremities. The results showed that the vitamin D supplementation group did not favor muscle strength in any of the examined muscle groups. There was a 4% decrease in muscle strength in the vitamin D supplementation group and 5% increase in the placebo group. The vitamin D supplementation group significantly reduced maximal muscle strength at handgrip by 9%. Knee flexion had a 19% increase in the placebo group and 6% increase in the vitamin D supplementation group. After adjusting for current smoking status, muscle strength results were not changed. Vitamin D supplementation group significantly increased in the time spent on performing the timed “up and go” test compared with placebo. In conclusion a high dose of Vitamin D supplementation had no beneficial effect on muscle function. Compared with placebo it was a small, but still a significant deterioration on some of the measurements of strength and physical performance. (Bisley, 2018)
9. Grimnes (2017) included 275 postmenopausal women aged 55-60 years in their randomized, double-blind controlled trial. Intervention group (N = 135) received vitamin D supplementation and control group (n = 140) received placebo. Muscle function was measured by handgrip, knee extension and balance. In this study they did not find any beneficial results between high doses of vitamin D supplementation and muscle function either. The conclusion is that one year with a high dose of vitamin D supplementation had no beneficial effect on muscle strength. (Grimnes, 2017)

Primary findings:

Even though not all of the studies agree upon the level of effect of HT, findings in this study indicate that HT alone has a beneficial effect on muscle function compared to non-HT. Combining HT with exercise is showing even greater effects than exercise/physical activity alone on a regular basis. Another method to check muscle function is with twitch, and our findings resulted in higher twitch in those who used HT. Estrogen therapy alone seems not to be beneficial on muscle function, and this needs further investigation. Vitamin D supplementation seems to be beneficial when it is given in moderate doses, but further studies are needed on vitamin D supplementation to say if it is beneficial.

Discussion

Bemben (2000) and Bondarev (2018) show that exercise has a beneficial effect on muscle function in menopausal women, both of them having a control group. Bemben (2000), the women in the high-load group are showing a better muscle strength, than the women in the high-repetition group in upper body strength. Bondarev (2018) study has a low age difference between the menopausal stages and this can cause significant interaction on muscle function. The data from Bondarev (2018) shows that the postmenopausal group had greatly weaker handgrip strength than the premenopausal group. Since the age difference was only 2 years apart between these two groups, it may indicate that the menopausal stages have an impact on muscle function and not only ordinary aging. (Bemben, 2000) (Bondarev, 2018). A gradual decrease in estrogen from the perimenopause is being replaced by an increase of estradiol. Understanding this to be a form of hormonal regulation and maintaining some hormonal balance.

Cangussu (2016) showed that it is an increase in muscle function with normal dose of vitamin D supplementation, but in Bisley (2018) and Grimnes (2017) they gave a high dose of Vitamin D supplementation to the intervention group. Their result showed that it is an decrease in muscle function for postmenopausal women, and the control group showed an increase in muscle strength without any supplementation and gaining greater results. (Cangussu, 2016) (Grimnes, 2017) Comparing these results it can be explained by fatigue or any other symptoms that might come with a high dose of vitamin D. Rejnmark (2011) is a systematic review that investigated if normal doses of vitamin D have an effect on muscle function. Their conclusion is that a normal dose of vitamin D has a beneficial effect on muscle

function, but they found more studies showing a lack of an effect. (Rejnmark, 2011) Further investigation is needed to confirm or reject Cangussu`s results.

Greising (2009) is a systematic review and meta-analysis study, about HT and skeletal muscle strength in postmenopausal women, who were on HT and nonusers. The HT contained Estradiol, estrone, estriol. Ten studies showed that HT-users had a modest but beneficial effect on muscle strength by 5%. Of the women using HT, the first-time users had the greatest effect when comparing them to those who had used HT before. The overall conclusion in this study is that HT were found to beneficially affect strength. In addition, they also concluded that adding resistance exercise training would increase muscular strength by 8%-14%. (Greising, 2009). Finni (2011), Taaffe (2005) and Ronkaine (2009) studies showed a result on how HT benefits muscle strength, and that this can be explained by the muscle fibers. It has been reported that type I muscle fibers seem to have more estrogen receptor messengers RNA (Ribonucleic acid), than type II muscle fibers, meaning type I fibers are more easily responsive to the estrogen hormone.

Then Greising (2009) compared mice and rats using estradiol. They found that mice had a greater effect on muscle strength than rats. The effect size for absolute strength was moderate but not statistically significant. The estradiol hormone had a larger effect on strength relative to the size of the muscle. After combining all the results for these rodents, they confirmed that estradiol as an ovarian hormone is in fact important for muscular strength. (Greising, 2009). Using rodents for these types of studies are great, neurologically being compared to humans. It is worth further research to see if this is relatable to postmenopausal women. It would have been interesting to know how the hormones individually would affect muscle function. Especially seems based on what we already know from Bemben and Langdon (2001) studied, that estrogen therapy has no useful effect on muscle function. Furthermore, estrogen and physical activity/exercise had no influence on hip bone mineral density, but estrogen therapy is advantages for bone mineral density and preventing osteoporosis.

Our findings indicate that HT has a beneficial effect on muscle function for women in menopause with/without exercise/physical activity. This can be caused by the hormonal secretion that helps to reduce menopausal symptoms, like insomnia and “hot flushes”. During sleep the secretion of growth hormone is highest and is stimulated by the tyroideahormones, androgens and estrogens, and this could explain why muscle function is better in women who

use HT. Sternfeld`s (2015) results showed that with aerobic exercise training for late peri- and postmenopausal women had an improvement in insomnia symptoms, sleep quality and depressive symptoms, but not alleviate vasomotor symptoms. (Sternfeld, 2015)
The growth hormone stimulates growth in body mass and length of the bones. The largest amount of cells in the pituitary anterior lobe are growth hormone producing cells, and that the secretion is highest at night. Hypothalamus produces the growth hormone- releasing hormone and the growth hormone- inhibiting hormone. The growth hormone stimulates cellular fat-combustion. Physical work, fasting, stress, low glucose concentration, and protein rich meals can result in an increased growth hormone-secretion. Cortisol can also inhibit the growth hormone-secretion.

Based on previous research used in this study, how the composition of vitamin D and hormones affect each other and varies in menopausal/postmenopausal women, may determine how one would treat the symptoms or decline in muscle function.

Conclusion.

After thorough research it is a reason to say that HT influences muscle function in menopausal women, both alone and combined with physical activity/exercise. During the menopausal transition, women have a significant decline in estrogen, but estrogen therapy alone had no beneficial effect on muscle function. Normal dose of vitamin D is optimal for muscle function, but not high dose. These findings are partly inconclusive and need further investigation.

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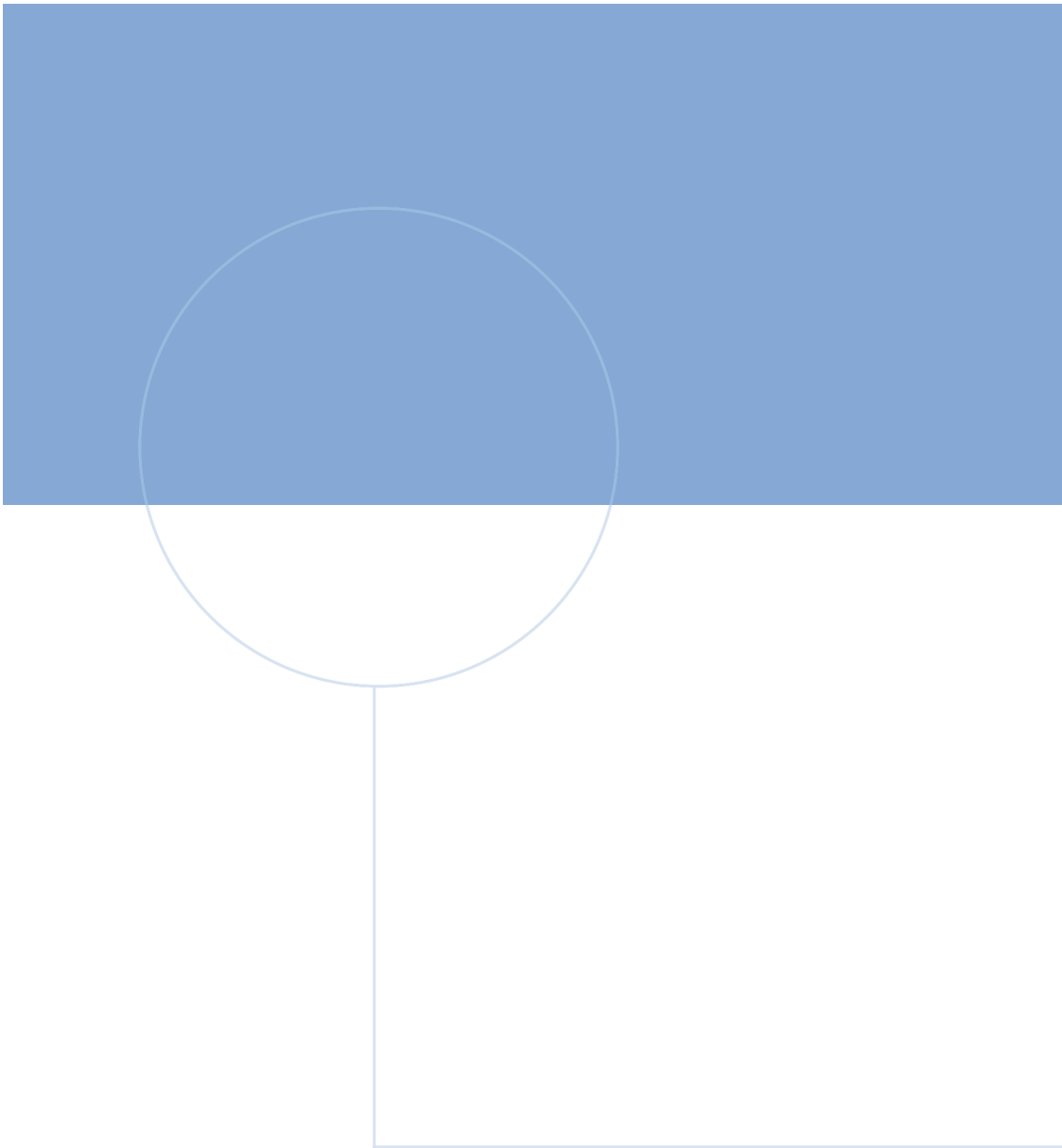

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